ARCHIVES of INTERNAL MEDICINE

VOLUME 65 APRIL 1940 NUMBER 4

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SUDDEN OCCLUSION OF CORONARY ARTERIES FOLLOWING REMOVAL OF CARDIO-SENSORY PATHWAYS

AN EXPERIMENTAL STUDY

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In a previous paper [1] experiments were reported showing that in dogs morphine and ether anesthesia markedly reduced the mortality rate after ligation of coronary arteries. In those experiments sudden death following ligation of the circumflex branch of the left coronary artery in the anesthetized dogs occurred in 25 per cent. Similar ligation in dogs in the conscious state resulted in a mortality rate of 75 per cent. Again, when ligation of the anterior descending branch of the left coronary artery was effected with anesthesia the mortality rate was less than 10 per cent, while similar ligation in conscious animals was followed by an increase in the mortality rate to approximately 40 per cent.

From direct and indirect observations on the conscious animals in that series of experiments it was suggested that in addition to the primary ischemic area produced by such ligation other areas of myocardium were rendered ischemic by a possible reflex spasm of the collateral coronary arteries and arterioles. The reflex mechanism was believed to be initiated by metabolites produced in the ischemic area initiating afferent impulses which, in turn, produced efferent vagal impulses, causing constriction of the medium-sized and smaller-sized coronary arteries. The marked reduction in mortality when ligation was performed with a surgical degree of anesthesia suggested that this reflex mechanism had been depressed.

Aided by a grant from the Josiah Macy Jr. Foundation, New York.

From the Department of Medical Research, Banting Institute, University of Toronto Faculty of Medicine.

1. Manning, G. W.; McEachern, C. G., and Hall, G. E.: Reflex Coronary Artery Spasm Following Sudden Occlusion of Other Coronary Branches, Arch. Int. Med. **64**:661-674 (Oct.) 1939.

We believe that this reflex mechanism alone is not completely responsible for the higher mortality in the conscious animal. As a result of our previous experiments it would appear, also, that certain areas of the myocardium are more readily influenced by ischemic processes than other regions and that ectopic beats, tachycardia and ventricular fibrillation are more readilly initiated when these highly irritable regions become ischemic.

We believe also that the degree of pain experienced by the animals after ligation of the coronary artery in the conscious state might play a part in increasing the mortality rate under these conditions. In this connection it is only necessary to mention here that the cardiosensory pathways are located in the cervical and thoracic cardiac nerves and pass through the stellate and upper five thoracic ganglions on their way to the spinal cord. After the complete removal of these ganglions animals should not experience any pain as a result of ligation of the coronary artery.

The purpose of the present paper is to report the results of experiments which show that the removal of the cardiosensory pathways protects the animal from pain and sudden death after ligation of the coronary artery in the conscious state.

Three groups of experiments were carried out in this series. In the first group partial cardiosensory denervation was produced by removal of the stellate and upper five thoracic ganglions on one side only. Pain was decreased, and the mortality following ligation of the large left circumflex branch was reduced. In the second group, in which complete cardiosensory denervation was produced, ligation of the smaller anterior descending branch resulted in no sudden deaths, and no pain was evidenced. In the third group complete cardiosensory ligation of the large left circumflex branch resulted in a marked decrease in the mortality rate, and again no pain was evidenced.

The possible clinical significance of this work will be discussed later in the paper.

EXPERIMENTS

Forty-six normal adult dogs used in this series were divided into three groups. In group 1 the left stellate and upper five thoracic ganglions were removed. At the same operation a loose ligature was placed around the circumflex branch of the left coronary artery close to its origin. The two ends of the loose ligature were brought to either end of the incision; the thorax was closed, and a sterile dressing was placed over the wound. The animal was allowed to recover from the anesthesia (morphine and ether). The following day ligation of the artery was effected by sudden traction on the ends of the ligature.

In group 2 the stellate and upper five thoracic ganglions were removed bilaterally. At a subsequent operation a loose ligature was

placed around the anterior descending branch of the left coronary artery, and the animals were then treated as in group 1.

The animals in group 3 were prepared in a similar manner to those in group 2 except that the circumflex branch of the left coronary artery was ligated.

Several normal electrocardiograms were taken on all dogs while they were lying on their right sides prior to any surgical intervention. Records were taken before, during and at varying intervals after ligation. In some instances continuous blood pressure recordings were made. Immediately autopsy was performed on all animals which died.

Although the surviving animals were kept quiet for a few hours, no attempt was made to limit their activities after this time. Some deaths from cardiac failure, resulting from overexertion in the presence of a damaged myocardium, would be expected. In spite of this eventuality deaths occurring within twenty-four hours of ligation were listed as "sudden deaths."

GROUP 1.—*Sudden occlusion of the left circumflex branch in animals following removal of the stellate and upper five thoracic ganglions on the left side.*

Twelve dogs were used in this group. Only slight cardiac pain was evidenced after sudden ligation of the artery in the conscious state. Dyspnea, restlessness, shock and sudden loss of consciousness were not observed in the animals which survived the sudden occlusion.

In this group 8 survived and 4 died within twenty-four hours. This gives a probable mortality rate of 33 per cent. One dog died in twenty-one hours and showed marked atelectasis on one side and pulmonary edema on the other. Two died in about four hours and showed definite signs of pulmonary congestion, some edema and engorgement of the right side of the heart. The fourth animal stopped breathing in nine minutes, and continuous electrocardiograms indicated a heart block (fig. 1).

Electrocardiographic Changes.—Within a few seconds of ligation there was an elevation of the RT segment, which became progressively more marked and reached its maximum within five minutes (fig. 2*B*). At this time a slight elevation of the RT segment was observed in lead I, while the elevation of this segment in leads II and III was so great that the T wave was hardly discernible.

The RT segment then began to recede toward the isoelectric level (fig. 2*C*). After a period of hours the Q wave increased in amplitude, and the RT segment in leads II and III remained elevated. The PR interval was normal (fig. 2*D*). The record taken one day after ligation showed a low voltage of the R wave and a widening of the QR interval in lead I (fig. 2*E*). The PR interval was irregular. After two days the RT segment was depressed and had assumed a rounded appearance.

Many of the typical abnormalities as seen in the later records persisted for from three weeks to three months.

GROUP 2.—*Sudden occlusion of the anterior descending branch in conscious dogs following bilateral removal of the stellate and upper five thoracic ganglions.*

Twelve animals were used in this group of experiments. The left anterior descending branch was ligated suddenly in the manner already described. Cardiac pain, dyspnea, restlessness or shock was not observed after the ligation. The

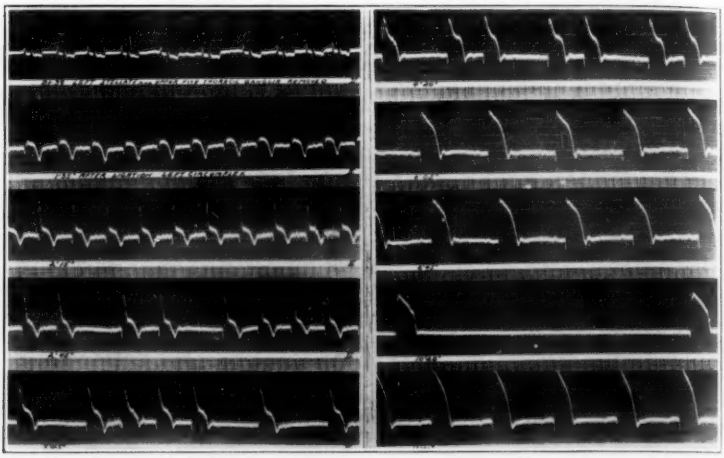

Fig. 1 (group 1).—Electrocardiogram (lead II) showing fatal heart block following ligation of the left circumflex branch after removal of the left stellate and upper five thoracic ganglions.

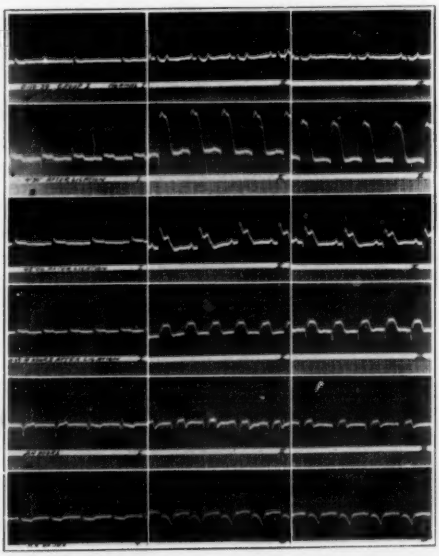

Fig. 2 (group 1).—Typical electrocardiogram (leads I, II and III) taken after ligation of the left circumflex branch after removal of the left stellate and upper five thoracic ganglions.

animals were exceedingly quiet, in contrast to animals in which similar ligations were carried out when the stellate and thoracic ganglions were intact.

Changes in blood pressure were not great. An initial decrease of about 20 mm. of mercury occurred some twenty seconds after ligation. However, within a few minutes the blood pressure had returned almost to normal.

No deaths occurred within twenty-four hours in this group. One animal died of infection on the third day; the remaining animals survived indefinitely. There were no deaths referable to the condition of the heart.

Electrocardiographic Changes.—The most characteristic features of the electrocardiographic records taken from the animals in this group were an elevation of the RT segment in lead I and a depression of the ST segment in leads II and III (fig. 3). This depression was apparent within a few seconds after ligation and

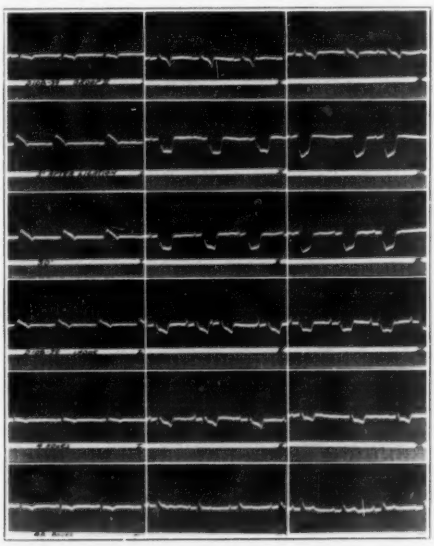

Fig. 3 (group 2).—Typical electrocardiogram (leads I, II and III) taken after ligation of the left anterior descending branch after removal of the stellate and upper five thoracic ganglions bilaterally.

reached its maximum in about five minutes. The depressed ST segment at this time showed an upward convexity. The depression became progressively less marked after ten minutes, and in about four hours the ST segment had returned almost to the isoelectric level, the T wave remaining markedly negative. The contour of the T wave changed during the next forty-eight hours, and at the end of this time the T wave was upright and of high amplitude. The records in all three leads were essentially normal within fourteen days.

GROUP 3.—*Sudden occlusion of the left circumflex branch in conscious animals following bilateral removal of the stellate and upper five thoracic ganglions.*

Twenty-two animals were used in this group of experiments. The artery was ligated in the conscious animals in the manner previously described. In only 2 animals was there any evidence of cardiac pain; both of these appeared to be

recovering, when suddenly ventricular tachycardia set in. Fatal ventricular fibrillation rapidly supervened, and the dogs died in nine and fifteen minutes, respectively, after ligation. Severe dyspnea in the absence of cardiac pain was observed in another case. This animal had prolonged and severe heart block which did not prove fatal (fig. 4).

No other animals died suddenly within twenty-four hours. The probable mortality rate was 9 per cent. The low mortality rate is of more significance in this group than in group 2, since the left circumflex branch supplies a much larger area of myocardium than does the anterior descending branch. Three delayed deaths occurred (within twenty-four to forty-eight hours) from cardiac failure, as indicated by pulmonary edema and congestion of the right side of the heart.

Electrocardiographic Changes.—With the exception of the 3 animals previously mentioned (the 2 dying with ventricular fibrillation and the 1 surviving a severe

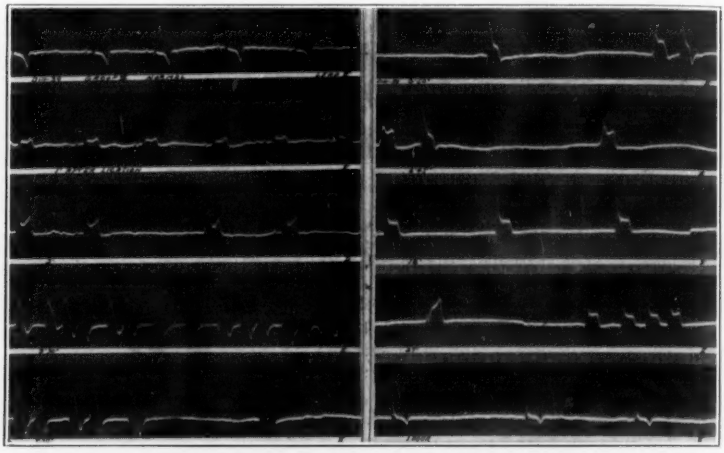

Fig. 4.—Electrocardiogram (lead II) showing severe heart block following ligation of the left circumflex branch after removal of the stellate and upper five thoracic ganglions bilaterally.

heart block) the electrocardiographic changes obtained in the animals in this group were uniform. The records of a typical experiment will be described.

A marked elevation of the RT segment occurred within thirty seconds (fig. 5) and was accompanied by a progressive increase in the amplitude of the ventricular complex, which reached its maximum in about five minutes (fig. 5*B*). The record taken at this time showed a high take-off of the RT segment, ending negatively in lead I. The high take-off of the elevated RT segment from the downstroke of the R wave was noticeable in leads II and III. The PR interval remained prolonged.

A few extrasystoles of left ventricular origin were noted periodically in leads II and III (fig. 5*C*). The PR interval was decreased.

No further significant changes in the electrocardiograms were noted until about six hours after ligation (fig. 5*D*). A few ventricular extrasystoles persisted, and a complete dissociation between auricular and ventricular complexes was found.

Further changes in the electrocardiographic record took place in twenty-four hours (fig. 5 *E*), after which time the form of the record became more stable, and at forty-eight hours the record was typical of axis deviation (fig. 5 *F*).

The time required for the electrocardiograms to return to normal varied in different animals. Changes could frequently be observed over a period of weeks.

COMMENT

In the experiments reported in this paper we have attempted to investigate further the reflex mechanisms which we believe to be responsible for the high percentage of sudden deaths following experimental ligation of large branches of the coronary artery in conscious animals.

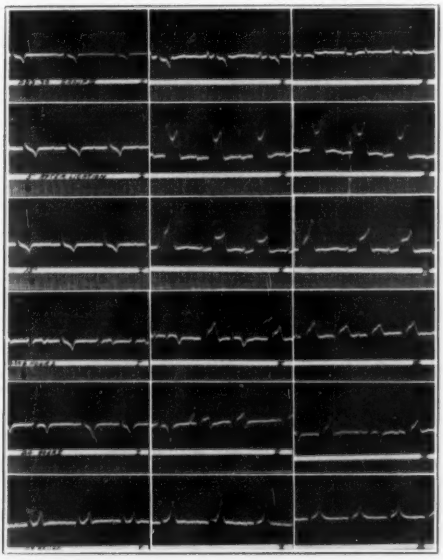

Fig. 5 (group 3).—Typical electrocardiogram (leads I, II and III) taken after ligation of the left circumflex branch after the removal of the stellate and upper five thoracic ganglions bilaterally.

In brief, we have previously shown that: (1) ligation of the left anterior descending branch in the anesthetized animal resulted in a mortality rate of less than 10 per cent, while ligation of the same branch in the conscious animal was attended by a mortality rate of about 40 per cent; (2) ligation of the larger left circumflex branch in the anesthetized animal resulted in a mortality rate of about 25 per cent, and when this ligation was performed in the conscious animal the mortality rate increased to 75 per cent, and (3) the animals which died

suddenly after the ligation of either the anterior descending or the circumflex branch in the conscious state all showed ventricular extrasystoles, tachycardia and terminal ventricular fibrillation (figs. 6 and 7).

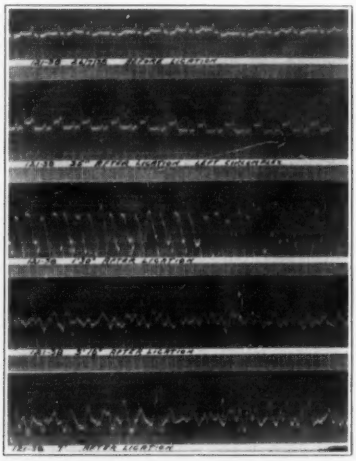

Fig. 6.—Electrocardiogram (lead II) showing fatal ventricular fibrillation following ligation of the left circumflex branch in a conscious animal.

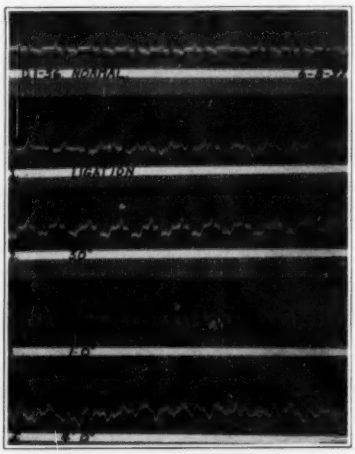

Fig. 7.—Electrocardiogram (lead II) showing fatal ventricular fibrillation following ligation of the left anterior descending branch in a conscious animal.

It is possible, however, that in a larger series of experiments some animals might have died suddenly from heart block.

It appeared from these experiments that the increased mortality following ligation in conscious animals was due to some reflex mechanism causing either spasm of collateral coronary arterioles or an altered irritability of the myocardium which permitted ventricular fibrillation to be more readily initiated.

This theoretic but possible reflex mechanism was apparently interrupted by the bilateral removal of the stellate and upper five thoracic ganglions, since the mortality following ligation of the larger left circumflex branch in the conscious animal was reduced from 75 per cent to 10 per cent as a result of such surgical intervention. Ventricular extrasystoles were present in only a few instances; ventricular tachycardia was infrequently noted, and ventricular fibrillation was observed in only the 2 dogs which died.

When the stellate and upper five thoracic ganglions had been removed on only the left side (group 1) acute ligation of the left circumflex branch in the conscious state resulted in a mortality rate of about 33 per cent. One of the animals dying while under observation showed electrocardiographic evidence of complete heart block (fig. 1). Ventricular fibrillation was not observed in any of the animals in this group. From this fact it was believed that even the removal of the cardiac sympathetic nerves on one side prevented to a great extent the mechanisms which may have been responsible for the high mortality rate following coronary artery ligation in intact conscious animals.

When the left anterior descending branch (group 2) was ligated after the bilateral sympathetic denervation of the heart the mortality rate was 0. Again, extrasystoles were relatively infrequent. Ventricular tachycardia and ventricular fibrillation were not observed.

It would appear that ablation of the cardiosensory pathways not only prevented pain after temporary coronary occlusion, as has been shown by White, Garrey and Atkins,[2] but also decreased materially the incidence of ventricular fibrillation and the mortality in animals after permanent occlusion. Again, it should be emphasized that the size of the infarcts produced in these animals was essentially the same as in the groups with intact cardiac sympathetic nerves after ligation of a similar coronary artery branch. The decrease in mortality possibly results from the interruption of the reflex arc, preventing afferent impulses from reaching the vasoconstrictor center and thus eliminating reflex spasm of collateral coronary arteries. On the other hand, it may be that sympathetic denervation has rendered the myocardium less susceptible to the onset of ventricular fibrillation. Possibly both mechanisms have been affected.

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2. White, J. C.; Garrey, W. E., and Atkins, J. A.: Cardiac Innervation: Experimental and Clinical Studies, Arch. Surg. **26**:765 (May) 1933.

On the basis of the anatomic distribution of the sympathetic nerves to the heart it appears that removal of the stellate ganglions would not be as effective in decreasing the mortality following ligation of the coronary artery as would a more complete sympathetic denervation of the heart.

It is important to mention in this connection that the sensory pathways lie in the thoracic cardiac nerves as well as in the inferior and middle cervical cardiac nerves. In order to abolish pain completely it is necessary to remove the whole sensory supply of the heart. It is possible that when the sensory pathways are completely interrupted the mechanism responsible for the onset of fatal ventricular fibrillation may likewise be eliminated to a great extent.

Although one should not, and in many cases cannot, apply to human beings the direct results of animal experimentation, it is, in this instance, tempting to try to correlate our experimental observations with clinical observations on patients with angina pectoris. In this connection there is the possibility that patients suffering from this condition as well as from coronary thrombosis have a particularly susceptible nervous system. Their reflex nervous mechanisms may perhaps be much more sensitive than those in the ordinary person. Mild or moderate exertion, cold air and emotion are some of the activities which may precipitate an attack of angina pectoris in a susceptible person, but it could hardly be said that the average person would likewise be affected.

Patients with angina pectoris have a life expectancy of approximately five years. In these patients the incidence of sudden death is high. In view of these two facts it does not seem unreasonable to assume that bilateral sympathetic denervation of the heart may still have a sound clinical application. Such surgical intervention might protect these patients from pain and at the same time from sudden death which so frequently occurs.

SUMMARY

Removal of the cardiosensory pathways eliminates the pain and markedly reduces the mortality rate after sudden and permanent occlusion of the larger branches of the left coronary artery in the conscious dog.

PROGRESS IN CHEMOTHERAPY OF BACTERIAL AND OTHER DISEASES

WITH SPECIAL REFERENCE TO THE PRONTOSILS, SULFANILAMIDE AND SULFAPYRIDINE

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Until the discovery of the effectiveness of the original prontosil (the hydrochloride of 4-sulfonamido-2′,4′-diaminoazobenzene) in the treatment of streptococcic and staphylococcic infections the chemotherapy of systemic bacterial diseases was largely disappointing. It is true that certain dyes, like gentian violet and acriflavine base as well as various mercurial compounds, commanded considerable attention and extensive clinical trial, with encouraging results in individual cases; but in general, original hopes and expectations were not realized. Indeed, aside from the helpful effects of neoarsphenamine in the treatment of anthrax and the clinically inapplicable treatment of pneumococcic infections with ethylhydrocupreine (optochin) base and its soluble derivative ethylhydrocupreine hydrochloride, the only site in which bacteria have been found vulnerable by systemic chemical attack has been the urinary tract, where conditions are exceptional. But, as I wrote in 1936:

> I by no means share the skepticism so frequently expressed in regard to the future of the chemotherapy of bacterial diseases if money and interested workers are available for the tremendous expense and labor required for advancing our knowledge. It is true that more, much more, advance has been made in the chemotherapy of protozoal and metazoal diseases and that the problems of bacterial diseases are apparently more difficult, but when one considers the advances made during the past five years it is neither rash nor unwise to expect greater discoveries in the future as the fruit of hard, conscientious and unremitting, but systematized toil coupled with the ever alluring chance of making a "lucky strike."

It is only a few years since this "lucky strike" was made, in the discovery of the remarkable chemotherapeutic properties of the prontosils and sulfanilamide, followed by sulfapyridine; and their known effective scope is widening so rapidly and with brilliant success in so many directions, yet with much ground remaining to be explored, that the ultimate consequences of their discovery cannot be predicted. Definite knowledge, however, has been masked by publications which are speculative, statistically vulnerable or so irrelevant as to be of little value; hence it appears that a review of the more recent literature bearing on the use of these

compounds in experimental infections and human disease may be helpful, particularly since only a few persons are in position to assimilate it except in predigested or concentrated form.

HISTORICAL SURVEY OF COMPOUNDS REVIEWED

Thirty-two years ago Gelmo synthesized paraaminobenzenesulfonamide, now universally known as sulfanilamide, but its medicinal value was neither suspected nor studied. In 1909 Hörlein, Dressel and Kothe (*Deutsches Reichpatent* 226230, 226235, 226239, 226240, 226594 and 22677) prepared azo dyes with sulfonamide and substituted sulfonamide groups, one of which possessed a limited therapeutic effect in experimental hemolytic streptococcic infections of mice but received little attention. Further investigation under Domagk resulted in the production of the hydrochloride of 4-sulfamido-2′,4′-diaminoazobenzene, a brick red powder relatively insoluble in water (0.25 per cent), which was included in the German patent granted Mietzsch and Klarer in 1932 (*Deutsches Reichpatent* 607537) covering several sulfonamide-containing azo dyes and to which the trade name "prontosil" was given. This has subsequently been designated as "the original prontosil" and, while no longer employed, has the distinction of being the compound used by Foerster in 1933, under the name "streptozon," in the first recorded instance of treatment of a human being (a child) with staphylococcic septicemia resulting in recovery. Doubtless the name used by Foerster was due to his knowledge of the fact that Domagk had employed the compound in 1932 in the treatment of experimental streptococcic infections of mice, although it was not until 1935 that Domagk published his epoch-making paper announcing the remarkable therapeutic effectiveness of the original prontosil not only on experimental streptococcic infections of mice and rabbits but to some extent on staphylococcic infections of rabbits as well, and thereby introducing to the world an agent constituting one of the greatest discoveries in the history of chemotherapy.

In the same issue of the *Deutsche medizinische Wochenschrift* appeared three clinical reports attesting the efficacy of the original prontosil in various streptococcic infections as well as in infections of the urinary tract due to the colon bacillus. Later in the same year Domagk announced a new soluble derivative, the disodium salt of 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′,6′-disulfonate, called prontosil S or prontosil soluble, which he stated was just as effective as the original prontosil in streptococcic and staphylococcic infections and also possessed a certain degree of therapeutic effect on pneumococcic infections of types I and II in mice; this compound is now marketed in the United States under the name of neoprontosil in tablets and in a 5 per cent solution.

In 1936 the Tréfouëls, Nitti and Bovet found that the effective azo dyes broke down in the tissues at the azo linkage to paraaminobenzenesulfonamide, the compound first synthesized by Gelmo in 1908, and suggested that the therapeutic effectiveness of the original and of the soluble prontosil was due to this white powder, which was called prontosil album and later since of worldwide renown, sulfanilamide, the name given it by the Council on Pharmacy and Chemistry of the American Medical Association on April 17, 1937. This discovery, coupled with the fact that it was not protected by patents, led rapidly to its widespread manufacture and use, as well as to the preparation and testing of a large number of various new derivatives, although clinical experience lends some support to Domagk's contention that the effectiveness of the prontosils is not entirely due to their reduction to sulfanilamide in the body, especially in certain streptococcic infections.

Expert chemists have carefully studied the chemical structure of many new derivatives but have been unable to learn what makes one compound more therapeutically active and less toxic than another closely related one. Thus, proseptasine or septazine (parabenzylaminobenzenesulfonamide; N^4-benzylsulfanilamide) is a compound in which substitution has been made in the amino group without superior properties, but this is a familiar story in chemotherapy, where Nature is loath to give up her secrets on chemical constitution in relation to disinfection. Indeed, only actual trials in the living animal for both toxicity and therapeutic effectiveness serve as criteria, and no one knows how many compounds are at present on the shelves of laboratories which may have valuable chemotherapeutic properties.

However, two compounds in which one hydrogen atom of the sulfonamide group has been substituted have been found highly effective, namely, sulfanilyldimethylsulfanilamide (known commercially chiefly as uleron or uliron) for gonococcic infections and sulfapyridine for pneumococcic infections. The former, which is paraaminobenzenesulfonylparaaminobenzenedimethylsulfonamide, is relatively insoluble in water and is administered orally, but a soluble sodium salt for parenteral administration is now available. The latter, which is 2-(paraaminobenzenesulfonamido)-pyridine and which is also sold commercially as M. & B. 693 and as dagenan, is likewise relatively insoluble in water, but a soluble sodium salt for parenteral administration has been prepared. In this connection it is interesting to note that Kolmer, Brown and Raiziss were first to use pyridine compounds in the chemotherapy of experimental streptococcic infections, of which one (2-2'-pyridyl sulfide dihydrobromide) was as effective as neoprontosil although not of the same structure as sulfapyridine, which is a combination of sulfanilamide with alphaaminopyridine.

For the purposes of this review, therefore, which is largely confined to those compounds which have been subjected to trial in the treatment of both experimental infections and various diseases, only the prontosils,[1] sulfanilamide, sulfanilyldimethylsulfanilamide and sulfapyridine are chiefly considered, because a review of results observed with the large number of allied compounds in experimental infections alone would add greatly to its length and lead me too far afield from clinical applications. Furthermore, no attempt has been made to review the entire vast literature on these particular compounds; I have tried only to include a sufficient number of the more important articles to justify an expression of opinion of their value in the treatment of various experimental and human infections. Detailed and excellent reviews in book form have been published by Mellon, Gross and Cooper and more recently by Long and Bliss.

THERAPEUTIC EFFECTS

Streptococcic Infections.—It is well proved that the prontosils, sulfanilamide and sulfapyridine are highly effective in the treatment of mice in which intraperitoneal inoculation with hemolytic streptococci belonging to group A of Lancefield has resulted in peritonitis with an associated septicemia (table 1). The most striking results have been observed with streptococci of high virulence for mice, because a minimal lethal dose of such organisms contains only a small number of cocci, and the prontosils, as well as sulfanilamide and sulfapyridine, act better on a sparse and scattered bacterial population than on highly concentrated masses of bacteria.

Furthermore, these compounds do not appear to be as readily acetylated in mice as in rabbits, with the result that more free sulfanilamide is available in the blood and tissues for bacteriostatic effects. This probably accounts for the fact that the prontosils and sulfanilamide have proved less effective in the treatment of intradermal beta hemolytic streptococcic infections of rabbits with associated septicemia and suppurative arthritis, as employed by Kolmer and Rule in 1937 for chemotherapeutic investigations, because they provided experimental lesions more closely resembling streptococcic infections of human beings.

Owing to the low virulence of nonhemolytic streptococci for mice and rabbits, neither compound has been generally employed in therapeutic tests. Muether and Kinsella found sulfanilamide effective in the

1. In the text and in the tables "original prontosil" refers to the hydrochloride of 4-sulfamido-2′-4′-diaminoazobenzene. "Soluble prontosil" and "neoprontosil" refer to disodium 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′,6′-disulfonate, which is now marketed under the proprietary name "neoprontosil." Since this review was prepared, the Council on Pharmacy and Chemistry of the American Medical Association has adopted "azosulfamide" as the nonproprietary name for the latter compound.

treatment of experimental bacterial endocarditis of dogs due to Streptococcus viridans, but, as will be shortly discussed, the prontosils, sulfanilamide and sulfapyridine have generally failed in the treatment of Streptococcus viridans endocarditis of human beings so far as complete recovery is concerned; the same is true of Streptococcus faecalis infections of the urinary tract.

Most experimental investigations have been conducted with group A streptococci. Whether or not sulfanilamide varies in effectiveness with the remaining groups cannot be stated except to mention that the results of in vitro studies have shown groups A and C most susceptible,

TABLE 1.—*Experimental Hemolytic Streptococcic Infections*

			Treated		Controls	
Authors	Compounds	Animals	Number	Percentage of Survivors	Number	Percentage of Survivors
Domagk.....	Original prontosil	Mice	12	100	..	....
Levaditi and Vaisman.	Original prontosil	Mice	8	37.5	3	0
Gley and Girard.....	Original prontosil	Mice	50	38	50	0
Buttle, Gray and Stephenson	Sulfanilamide and derivatives	Mice	138	43	96	0
Cooper, Gross and Lewis	Sulfanilamide	Mice	44	65	44	2.7
Long and Bliss.....	Soluble prontosil	Mice	84	37	64	0
Long and Bliss.....	Sulfanilamide	Mice	18	67	..	....
Raiziss, Severac, Moetsch and Clemence	Sulfanilamide	Mice	55	64 to 66	100	0
Raiziss, Severac, Moetsch and Clemence	Soluble prontosil	Mice	55	28 to 63	..	....
Raiziss, Severac, Moetsch and Clemence	Sulfanilamide	Mice	60	74	..	....
Raiziss, Severac, Moetsch and Clemence	Sulfanilamide	Mice	150	37 to 60	..	....
L. E. H. Whitby.....	Sulfapyridine	Mice	156	3.1-7 days	126	0.4-1.7 days
Kolmer, Raiziss, Rule and Brown	Soluble prontosil	Mice	12	50	8	0
Kolmer, Raiziss, Rule and Brown	Soluble prontosil	Rabbits*	3	Effective	..	....
Kolmer, Raiziss, Rule and Brown	Sulfanilamide	Rabbits*	45	Effective	..	....

* Intradermal lesions and arthritis.

groups B, E and G variable and group D quite insusceptible. Lockwood, Coburn and Stokinger, however, reported that no type seemed refractory to the compound in human infections and that groups C and G as well as group A seemed to be influenced by sulfanilamide therapy.

Hemolytic Streptococci: In this connection the studies of Spaulding and Bondi in my laboratory are also significant in indicating that infections with anaerobic hemolytic streptococci of mice are much less susceptible to the therapeutic activity of sulfanilamide and sulfapyridine than infections with aerobic strains. Since temporarily or permanently anaerobic hemolytic streptococci may be found in a large percentage of hemolytic streptococcic infections in human beings, this may offer an explanation of the failure of sulfanilamide and sulfapyridine in the

treatment of some cases of puerperal sepsis and other hemolytic streptococcic infections, as stated by Colebrook and Kenny. Thus an obligate anaerobic hemolytic streptococcus of group A was found highly insusceptible to sulfanilamide and sulfapyridine in the treatment of infections of mice, while a second strain was found moderately susceptible. A strain which was temporarily anaerobic, however, was moderately responsive to both compounds.

From the experimental standpoint it is difficult to draw any conclusions on the comparative therapeutic effects of the prontosils, sulfanilamide and sulfapyridine in the treatment of hemolytic streptococcic infections of mice. In terms of the actual amounts given in grams per kilogram of body weight, however, both the prontosils and sulfapyridine appear to be somewhat more effective than sulfanilamide. Of additional interest and importance is the question of simultaneous administration of antistreptococcus serum. Loewenthal has recently stated that the combination treatment with serum and sulfanilamide for streptococcic infections of mice gave better results than either alone and that these two therapeutic agents act in a different but complementary manner.

Since the prontosils and sulfanilamide were first identified with the treatment of streptococcic infections in human beings, it is to be expected that the largest part of the literature has been devoted to them. One unfortunate result has been the indiscriminate use of these compounds in the treatment of all sorts of infections on the basis of clinical rather than bacteriologic diagnosis. As expected under the circumstances, infections due to nonhemolytic types of streptococci have been included, although fortunately most serious streptococcic infections of human beings are due to hemolytic streptococci of group A. As a result there is a greater uniformity of opinion regarding the effectiveness of the prontosils, sulfanilamide and sulfapyridine in the treatment of severe infections, especially septicemia, including puerperal sepsis, surgical cellulitis and lymphadenitis and erysipelas, than of minor infections.

(*a*) Puerperal Sepsis. Among the first to attract favorable attention was the treatment of puerperal fever with the original and soluble prontosils and sulfanilamide by Colebrook and Kenny, who reported a mortality of about 4.7 per cent in 64 patients and later about 7 per cent in 115 patients treated with sulfanilamide (table 2), as contrasted with a mortality of about 22.8 per cent when former methods of treatment were used. These results have been generally confirmed and have proved the great value of the compounds in the treatment of puerperal endometritis due to hemolytic streptococci, as well as in postabortal septicemia, especially since most of the deaths were mainly due to causes beyond the influence of treatment, such as pulmonary and cerebral embolism and hemorrhage. In addition to reduction in mortality there has been

a distinct reduction in the average time of illness and the frequency of general peritonitis, and apparently Colebrook is of the opinion that the soluble prontosil (neoprontosil) may be more effective than sulfanilamide.

TABLE 2.—*Systemic Streptococcic Infections*

Authors	Diseases	Compounds	Number of Patients	Results
Colebrook and Kenny.....	Puerperal sepsis	The prontosils and sulfanilamide	115	93 per cent recoveries
Foulis and Barr.....	Puerperal sepsis	Soluble prontosil and sulfanilamide	22	98.6 per cent recoveries
Snodgrass and Anderson.....	Erysipelas	The prontosils and sulfanilamide	135	Effective
Nelson, Rinzler and Kelsey...	Erysipelas	Sulfanilamide	344	97.38 per cent recoveries
Sako, Dwan and Platou.....	Scarlet fever	Sulfanilamide	100	Reduction in complications
Peters and Howard.....	Scarlet fever	Sulfanilamide	150	Reduction in complications
Colebrook and Kenny.....	Puerperal peritonitis	The prontosils	10	90 per cent recoveries
Hageman and Blake.....	Pneumonia	Sulfanilamide	7	100 per cent recoveries
Major and Leger.....	Subacute endocarditis*	Soluble prontosil	1	Alleged effective
Klee and Römer.....	Subacute endocarditis	Original prontosil	5	Ineffective
Ellis.....	Subacute endocarditis	Sulfapyridine	2	Temporarily improved
L. Whitby.....	Subacute endocarditis	Sulfapyridine	3	Temporarily improved
Barnett, Hartman, Perley and Ruhoff	Subacute endocarditis	Sulfapyridine	1	Temporarily improved
Sailer.....	Subacute endocarditis	Sulfanilamide	1	Ineffective
Kelson and White.....	Subacute endocarditis	Sulfapyridine and heparin	1	3 apparently cured
Bliss, Long and Feinstone...	Subacute endocarditis	Sulfanilamide	3	No recoveries
Spink and Crago.....	Subacute endocarditis	Sulfanilamide	11	1 apparently cured
Bannick, Brown and Foster..	Ulcerative colitis	Neoprontosil and sulfanilamide	9	Effective
Collins.....	Ulcerative colitis	Sulfanilamide	11	Favorable in 73 per cent
Brown, Herrell and Bargen..	Ulcerative colitis	Neoprontosil	8	Favorable

* Due to Streptococcus viridans.

(*b*) Septicemia. Excellent results have also been reported in the treatment of hemolytic streptococcic septicemia of surgical origin complicating wounds and burns, with associated lymphadenitis. My personal experience in 18 cases during the past three years has been favorable. In each case there were one or more positive blood cultures. Recovery occurred in 14 cases, with a mortality of about 22 per cent. Treatment consisted of surgical drainage and oral administration of neoprontosil

and sulfanilamide, along with blood transfusions and intravenous administration of antistreptococcus serum.

(*c*) Erysipelas. There is almost complete unanimity of opinion on the uniformly good results observed in the treatment of simple uncomplicated erysipelas of both adults and children. In general terms the mortality in adults treated with antitoxin has been about 10 per cent and in infants and children, from 30 to 50 per cent, whereas after treatment with the prontosils and sulfanilamide these rates have been reduced to about 2 and 5 to 12 per cent, respectively. This may be due in large part to the vascularity of the lesions, which allows good access of free sulfanilamide in the blood. Such results are certainly much more favorable than those in cases in which there is some other complicating condition, like abscess or septic thrombi, in which the mortality has continued high in spite of neoprontosil and sulfanilamide therapy.

(*d*) Scarlet Fever. In cases of scarlet fever the compounds have not materially shortened the duration of fever or shown any marked effects on the rash; nor are such effects to be expected, since sulfanilamide apparently possesses but feeble neutralizing or inactivating power on exogenous toxins, including most likely the erythrotoxin of this disease. The compounds have apparently proved of value, however, in materially reducing the percentage of complications, like otitis media, mastoiditis, lymphadenitis and nephritis, by inhibiting the aggressiveness of the streptococci. For this reason it appears that the treatment of scarlet fever, in so far as specific therapy is concerned, may consist in the administration of convalescent serum or antitoxin for combating the early toxemia of the disease and of neoprontosil or sulfanilamide for combating the invasiveness of the streptococci themselves.

(*e*) Meningitis. One of the most impressive results observed with neoprontosil and sulfanilamide has been in the treatment of streptococcic meningitis (table 3), with which the mortality has been hitherto almost 100 per cent. Kolmer, Rule and Werner treated 46 rabbits with experimental hemolytic streptococcic meningitis with sulfanilamide and recorded the recovery of 20 per cent, whereas all of 12 untreated controls succumbed; of 12 monkeys 58 per cent recovered, with fatal results in 2 untreated controls. Of course, nothing else of value in the treatment of this highly mortal disease can be overlooked, especially adequate drainage of the primary foci of infection, so likely to be mastoiditis or sinusitis, along with drainage of the cerebrospinal fluid every eight to twelve hours. Oral or parenteral administration is preferred; it is doubtful if intrathecal injections of the compounds are indicated, although both neoprontosil and sulfanilamide are well borne by this route of administration. Apparently sulfanilamide is the compound of choice. While streptococcic meningitis is usually due to hemolytic types, a few patients

recovering under sulfanilamide therapy are believed to have had conditions due to nonhemolytic types, including Str. viridans; however, the condition may have been really caused by a hemolytic streptococcus stabilized in the viridans phase. My personal experience is confined to 5 cases, in which the condition was secondary to mastoiditis or nasal accessory sinusitis and in which sulfanilamide was administered, with 3 recoveries.

(*f*) Tonsillitis, Pharyngitis, Laryngitis and Cervical Adenitis. Many authors have reported favorable results in the treatment of acute tonsillitis, pharyngitis and laryngitis, but extensive studies are few. In many cases, however, no improvement has been shown, and certainly neoprontosil and sulfanilamide by oral administration and local application

TABLE 3.—*Streptococcic Meningitis*

Authors	Compounds	Number of Patients	Percentage of Recoveries
Schwentker and others	Sulfanilamide	4	75
Neal and Applebaum	Soluble prontosil	17	76
Neal	Sulfanilamide	26	81
Trachler, Frauenberger, Wagner and Mitchell	Sulfanilamide	7	57
Cawthorne	Sulfanilamide	3	66
Smith and Coon	Soluble prontosil and sulfanilamide	2	100
Sappington and Favorite	Sulfanilamide	6	67
Carey	Sulfanilamide	4	100
Toomey and Kimball	Sulfanilamide	12	83.4
Love	Sulfanilamide and neoprontosil	1*	Recovered
Applebaum	Sulfanilamide and neoprontosil	3*	33.3
Anderson	Soluble prontosil and sulfanilamide	1	Recovered
Arnold	Sulfanilamide	1	Recovered
Smith and others	Sulfanilamide	1	Recovered

* Nonhemolytic streptococcic infections.

have proved ineffective in the treatment of carriers. Some patients with cervical adenitis have improved rapidly, with cessation of fever and complete reduction in swelling, while others have shown no change and have required incision and drainage of the infected glands.

(*g*) Sinusitis. Good results have also been reported in cases of acute sinusitis due to hemolytic streptococci, but the results in cases of chronic sinusitis have been largely disappointing, probably because so many of the chronic conditions are due to staphylococci, pneumococci or nonhemolytic streptococci or represent mixed infections.

(*h*) Otitis Media and Mastoiditis. Variable and unpredictable results have been reported in cases of acute otitis media and mastoiditis. In some rapid improvement has been shown and in others, none. In still others the infection has progressed to mastoiditis, requiring operation. However, it has been observed that more prompt healing of the mastoid

wound takes place when the patient is receiving sulfanilamide, and postoperative care is shortened and simplified. Maybaum, Snyder and Coleman, however, have stated that sulfanilamide may mask infections of the mastoid or render them latent and thereby add to the difficulty of diagnosis.

(*i*) Peritonitis. In cases of idiopathic streptococcic peritonitis of children, in which the mortality has varied from 54 to 100 per cent, the compound has been of value; Ladd, Botsford and Curnen reported recovery in 5 of 7 cases. Stewart and Bates have also recorded recovery in 1 case.

(*j*) Other Infections. Favorable results have also been observed in cases of Ludwig's angina, streptococcic pneumonia and empyema, cellulitis and lymphadenitis and burns, as well as in cases of osteomyelitis, although sulfanilamide is usually ineffective in the presence of necrotic bone, as in chronic otitis media. As reported by Lockwood and his colleagues, sulfanilamide has shown striking differences in therapeutic effectiveness against hemolytic streptococcic infections in relation to the clinical character of the infection, being most effective for septicemia, lymphangitis, erysipelas, cellulitis and early infections with little suppuration and frequently ineffective when abscesses are well established and also in wounds where the presence of debris, human or bacterial, in the form of necrotic tissue inhibits its activity. In this connection, reference may be made to the observations of Bricker and Graham, who found that sulfanilamide tended to inhibit the healing of experimental uninfected wounds of dogs, which may have a bearing on the prophylactic use of the compound.

Nonhemolytic Streptococci: While the prontosils and sulfanilamide have usually proved ineffective in infections due to nonhemolytic streptococci, encouraging results have been reported in the treatment of ulcerative colitis, especially with neoprontosil by oral administration one hour before meals, which has been found better tolerated than sulfanilamide. Unfortunately, both have usually proved ineffective in the treatment of patients with Streptococcus viridans endocarditis with positive blood cultures, so far as complete recovery and survival are concerned, although both, and especially sulfapyridine, have produced improvement in some instances in the way of temporarily sterile blood cultures and reduction of fever while large doses were being given. I have seen 2 patients with typical symptoms and signs but with sterile blood cultures, similar to those described by Keefer, make complete recoveries after treatment with neoprontosil, but in the absence of positive blood cultures one cannot be sure that recovery may not have occurred just as well without this treatment. Whether or not sulfapyridine and especially its soluble sodium salt given by intravenous

injection will prove effective remains to be determined, but the compounds are probably more hopeful and worthy of trial in cases of this highly mortal disease. All of 10 patients in my own practice treated with sulfanilamide and sulfapyridine over two to five months ultimately perished of the disease, although I thought that life was prolonged in all. At the present time interest in the treatment of this highly mortal disease with orally administered sulfapyridine combined with the intravenous administration of heparin has been greatly renewed by the encouraging report of Kelson and White.

Meningococcic Infections.—That sulfanilamide protects a large percentage of mice in experimental meningococcic infections was first observed by Buttle, Gray and Stephenson and confirmed by Proom, using Miller and Castle's method of intraperitoneal inoculation in mucin.

TABLE 4.—*Experimental Meningococcic Septicemia*

Authors	Compounds	Treated		Controls	
		Mice, Number	Percentage of Survival	Number	Percentage of Survival
Buttle, Gray and Stephenson....	Sulfanilamide	30	76.6	30	6.6
Proom.....	Sulfanilamide	270	84.4	270	13.7
Rosenthal.....	Sulfanilamide	35	31.4	35	0
Branham and Rosenthal.....	Sulfanilamide	265	70.6	265	8.7
Brown.....	Sulfanilamide	76	38.2	30	0
Bliss, Feinstone, Garrett and Long.....	Sulfanilamide	50	24	30	0
Bliss, Feinstone, Garrett and Long.....	Sulfapyridine	50	16	..	....
McKee, Rake, Greep and Van Dyke.....	Sulfathiazole*	29	40	29	0
McKee, Rake, Greep and Van Dyke.....	Sulfapyridine	28	28.5	..	....

* 2-(paraaminobenzenesulfonamido)-thiazole.

These observations were soon confirmed by Levaditi and Vaisman and others (table 4) with sulfanilamide and various derivatives. According to Brown and to Branham and Rosenthal, combined sulfanilamide and serum treatment is more effective in mice than either alone. Branham has recently reported that weight for weight sulfapyridine showed a protective action against meningococcic infections in mice about ten times that of sulfanilamide under the conditions of the experiments and that the combination of either of the two compounds with serum consistently gave results far better than those obtained with either compound alone.

Clinical reports have also shown that sulfanilamide is highly effective in the treatment of meningococcic meningitis (table 5) and is probably the compound of choice, since neoprontosil penetrates far less rapidly. Indeed, on the basis of mortality rates, the results have been equal to and in some instances decidedly better than those observed with serum treatment, and sulfapyridine may be even more effective than

sulfanilamide. The optimum method of administration, however, and the indications for serum treatment in addition are not yet agreed on and must be decided according to conditions in individual cases. In so far as serum is concerned, there are the questions of route and dose as well as the difficult choice of which type of serum, antitoxic or antibacterial, should be used. As previously stated, experimental evidence indicates that sulfanilamide and serum are more effective than either alone, and clinical evidence is in favor of combining intravenous or intraperitoneal serum therapy with administration of the drug in cases of severe infections.

But in cases of mild or average infections sulfanilamide in maximum dosage by oral administration alone appears to be sufficient when a

TABLE 5.—*Meningococcic Meningitis and Chronic Septicemia*

Authors	Compounds	Number of Patients	Percentage of Recoveries
Schwentker and others	Sulfanilamide	52	85
Banks	Sulfanilamide	16	94
Banks	Sulfanilamide and sulfapyridine	72	98.6
Hobson and MacQuaide	Sulfapyridine	6	100
Jewesbury	Sulfanilamide	6	100
Eldahl	Sulfanilamide	12	75
Willien	Sulfanilamide	5	100
Somers	Sulfanilamide	143	90
Bryant	Soluble prontosil and sulfanilamide	21	95
Bryant	Sulfapyridine	168	95
Sappington and Favorite	Sulfanilamide	8	75
Muraz, Chirie and Queguiner	Sulfanilamide	54	85.2
Muraz, Chirie and Queguiner	Sulfanilamide	271	89.3
Waghelstein	Sulfanilamide	72	84.7
Dimson	Sulfapyridine	1*	Recovery
Zendel and Greenberg	Sulfanilamide	1*	Recovery

* Chronic meningococcic septicemia.

concentration of at least 5 mg. of free sulfanilamide per hundred cubic centimeters of spinal fluid can be secured and maintained for at least three days. For comatose patients and when vomiting renders oral medication impossible parenteral administration is required. Whether or not intrathecal injections of sulfanilamide are helpful in addition cannot be stated, but they are apparently worthy of trial in the treatment of severe infections, especially as a preliminary injection, and when the concentration in the spinal fluid from enteral and parenteral administration is low.

Sulfanilamide and sulfapyridine are likewise indicated in the treatment of chronic meningococcic septicemia, a condition likely to be the result of persistent meningococcic infection of the nasal accessory sinuses and characterized by recurrent chills and fever, crops of cutaneous nodules, arthralgia and positive blood cultures; this disease has an unfavorable prognosis and serum treatment has generally failed.

Pneumococcic Infections.—Soluble prontosil was originally stated by Domagk, in 1935, to have an effect on experimental pneumococcic infections of types I and II in mice, and his results were soon confirmed

TABLE 6.—*Experimental Pneumococcic Infections*

Authors	Compounds	Animals	Pneumococcus, Types	Treated		Controls	
				Number	Percentage of Survivors	Number	Percentage of Survivors
Rosenthal	Sulfanilamide	Rats	I, II and III	30	90	30	0
Rosenthal	Sulfanilamide	Rabbits	I	10	80	10	0
Cooper, Gross and Lewis	Sulfanilamide	Mice	II, III, VII and XXII	83	0 to 90	101	0 to 30
Cooper, Gross and Mellon	Sulfanilamide	Rats	I and III	101	20 to 80	75	0 to 45
Cooper, Gross and Mellon	Sulfapyridine	Mice	II and XXII	60	37 to 45	50	0
Buegsegger and Hamburger	Sulfanilamide	Mice	I, II, III and VIII	212	1 to 3	129	0
Schmidt	Sulfanilamide	Mice	XIV	40	50	8	0
Whitby	Sulfanilamide	Mice	I, II, III, V, VII and VIII	667	0 to 7 days	180	9.7 in 3.3 days
Raiziss, Severac, Moetsch and Clemence	Sulfanilamide	Mice	II	45	0	80	0
Raiziss, Severac, Moetsch and Clemence	Sulfapyridine	Mice	II	50	8	...	...
Raiziss, Severac, Moetsch and Clemence	Sulfanilamide	Mice	I, II and III	150	0 to 3	...	...
Raiziss, Severac, Moetsch and Clemence	Sulfapyridine	Mice	I, II and III	220	0.9 to 13.3	...	...
Bliss, Feinstone, Garrett and Long	Sulfanilamide	Mice	I, II and III	125	0	75	0
Bliss, Feinstone, Garrett and Long	Sulfapyridine	Mice	I, II and III	125	0.8	...	...
Kepl and Gunn	Sulfapyridine	Rats	I	81	32	57	0
Kepl and Gunn	Sulfanilamide and sulfapyridine	Rats	III	49	25	33	3
Bieter, Larson, Levine and Cranston	Sulfapyridine	Mice	II	90	44 to 63.4	100	0
Kolmer, Raiziss and Rule	Sulfanilamide	Rats	I, II and III	72	32	18	0
Kolmer, Raiziss and Rule	Sulfanilamide	Rabbits*	I, II and III	51	Effective	24	0
Kreidler	Sulfanilamide	Rabbits*	I	22	32	14	0
Larson, Bieter and Levine	Sulfapyridine	Rabbits	II	25	76	23	4.2
Havens, Hansen and Kramer	Sulfapyridine	Rabbits	I	20	45	20	30
Gregg, Loosli and Hamburger	Sulfapyridine	Dogs†	I	24	100	32	50
McKee, Rake, Greep and Van Dyke	Sulfathiazole	Mice	I, II and III	87	20.7	60	0
McKee, Rake, Greep and Van Dyke	Sulfapyridine	Mice	I, II and III	90	44.4	..	...

* Intradermal infections.
† Pneumonia.

by Hörlein. Subsequent studies (table 6) on pneumococcic peritonitis and septicemia of mice, intradermal infections of rabbits and pneumonia of rats and dogs have shown that sulfanilamide and especially sulfapyri-

dine are decidedly effective against many types of pneumococci, including type III, which is the only one entirely uninfluenced by serum. MacLean, Rogers and Fleming recently showed that pneumococci vary in their sensitivity to sulfapyridine, and they described a test for such sensitivity; the variation is associated not with the type but with the individual strain. Ross reported a case in which pneumococcic meningitis was fatal in spite of treatment with sulfapyridine; he thought that

TABLE 7.—*Pneumococcic Pneumonia*

Authors	Compounds	Types	Number of Patients	Percentage of Recoveries
Evans and Gailsford	Sulfapyridine	I, II, III and group IV	100	92
Finland and Brown	Sulfanilamide	I, II, V and VII	19	20 to 62.5
Price and Myers	Sulfanilamide	29 types	115	84
Traut and Logan	Sulfanilamide	Not stated	9	70
Flippin and Pepper	Sulfapyridine	I, II, III, IV, V, VI, VII and VIII	102	96 to 100
Anderson and Dowdeswell	Sulfapyridine	Various	100	98
Agranat, Dreosoti and Ordman	Sulfapyridine	Various	280	96.4
Plummer and Ensworth (a)	Sulfapyridine	Various	157	91.5
Alsted	Sulfapyridine	III	8	50
Smith and Needles	Sulfapyridine	Various	50	92
Pepper, Flippin, Schwartz and Lockwood	Sulfapyridine	I, II and III	400	93
Schwartz et al	Sulfapyridine	23 types	233	91
Plummer and Ensworth (b)	Sulfapyridine	26 types	270	87.4
Anderson, Cooper, Cairns and Brown	Sulfapyridine	II	70	91
Dowling and Abernethy	Sulfapyridine	26 types	136	89
Dowling and Abernethy	Serum	26 types	96	83.3
Nichol	Sulfapyridine	Not stated	2*	100
Barnett, Hartman, Perley and Ruhoff	Sulfanilamide	I, IV, VI, XI and XIV	43*	100
Wilson and others	Sulfapyridine	25 types	35*	Favorable
Smith and Nemir	Sulfapyridine	21 types	93*	93.5

* Infants and children.

the organism had acquired a tolerance for the compound. MacLeod and Daddi have succeeded in rendering a strain of type I pneumococcus "sulfapyridine fast" in vitro and in vivo, and MacLeod found the pneumococcus associated with a marked diminution in the production of hydrogen peroxide in cultures.

Pneumonia: While sulfanilamide has apparently been somewhat effective in the treatment of pneumococcic pneumonia there can be no doubt about the remarkable therapeutic efficacy of sulfapyridine in the treatment of lobar pneumonia and bronchopneumonia of various types in adults and in children (table 7). The first report was made by Evans and Gailsford, with a mortality of 8 per cent in 100 cases, as

compared with a mortality of 27 per cent in a control group of equal size. Indeed, it appears that the mortality in adults has been lowered to between 5 to 10 per cent, and equally favorable results have been observed in children. Furthermore, if the parenteral administration of sodium sulfapyridine fulfils present expectations, the mortality is likely to be still further reduced, since blood levels of 5 to 8 mg. per hundred cubic centimeters can be attained with great speed and certainty.[2] Parenteral medication is advisable not only in cases in which administration of sulfapyridine by mouth is impossible or in which intestinal absorption is poor but also in cases in which prompt action of the drug is imperative; however, it should be limited to conditions in which oral administration is impossible or does not suffice for successful therapy.

A critical reduction in temperature within twenty-four to forty-eight hours has been commonly observed, generally accompanied by a diminution of toxemia and an improvement in general well-being but not usually accompanied by any significant change in the pulmonary signs. In pneumococcic empyema, however, sulfapyridine is only doubtfully effective, in spite of the fact that the compound may be found in the exudate in a concentration similar to that in the blood. The cause of this reduced therapeutic effectiveness is not understood at present, but it may be the anaerobic conditions of the closed pleural sacs.

As a result of the favorable experience with sulfapyridine, the specific treatment of pneumonia has been simplified, and the costs of treatment have been greatly reduced. But the administration of type-specific serum may be required in those instances in which the patient fails to show clinical improvement within twenty-four to thirty-six hours with adequate dosage of sulfapyridine, especially when positive blood cultures are observed. The use of serum has been advised by Finland and Brown as an adjunct in the treatment of pneumonia in patients over 40 years of age or during pregnancy or the puerperium, when treatment is begun after the third day of illness and when more than one lobe is involved. In other words, sulfapyridine renders pneumococci more susceptible to immune bodies, and the administration of type-specific immune serum is most likely required in addition to sulfapyridine in the treatment of severe infections. MacLeod, summarizing work done at the Hospital of the Rockefeller Institute of Research, expressed the opinion that such synergism exists. Groups of mice were infected with pneumococci of type III and treated, respectively, with sulfapyridine alone, serum alone and the same amount of the two agents in combination. The results showed that type III antipneumococcus serum and sulfapyridine are synergistic,

2. Marshall and Long. Gailsford, Evans and Whitelaw.

since amounts of each agent which used singly exerted little or no protective action afforded protection to 60 per cent of the mice when used in combination. Similar results have been reported by Powell and Jamieson in the treatment of rats infected with pneumococci of types I, II, V, VII, VIII and XV.

A combination of sulfapyridine and antipneumococcus serum accompanied by adequate supportive measures and close clinical surveillance and aided by sputum typing, blood culture, daily blood counts and urinalyses apparently offers the best prognosis in the treatment of pneumonia. Serum has ceased to be expensive, as prices have again been lowered, and when sulfapyridine is used the recommended dose of serum is reduced 50 per cent. Possibly the use of parenteral injections of sodium sulfapyridine in addition to its oral administration will still further reduce the need for supplemental serum therapy.

TABLE 8.—*Experimental Pneumococcic Meningitis*

				Treated		Controls	
Authors	Compounds	Types	Animals	Number	Percentage of Survivors	Number	Percentage of Survivors
Kolmer, Rule and Werner	Sulfanilamide	I, II and III	Rabbits	60	0	12	0
Kolmer, Rule and Werner	Sulfanilamide	I, II and III	Monkeys	10	10	4	0
Cooper, Gross and Lewis	Sulfanilamide	II	Rats	47	50 to 73.3	36	0
Cooper, Gross and Lewis	Sulfapyridine	II	Rats	30	57	16	0
Gross, Cooper and Lewis	Sulfanilamide	II	Rats	15	59.5	37	0

Meningitis: Even more dramatic success has been observed in the treatment of pneumococcic meningitis, with which the mortality has been hitherto practically 100 per cent. In experimental pneumococcic meningitis of rabbits Kolmer, Rule and Werner found sulfanilamide ineffective, although in 10 monkeys treated there was 1 recovery. In rats, however, Cooper, Gross and Lewis and later Gross, Cooper and Lewis observed much better results with both sulfanilamide and sulfapyridine (table 8).

A shown in table 9, the use of these compounds has materially reduced the mortality from human infections, and sulfapyridine is undoubtedly the compound of choice. My personal experience is limited to 3 cases of a condition of otitic origin in which sulfapyridine was administered, with 1 recovery. Adequate and prompt surgical drainage of primary foci of infection is important when possible, along with spinal drainages at frequent intervals; and, needless to state, maximum doses of sulfapyridine are indicated in order to bring the concentration of free compound to at least 5 mg. per hundred cubic

centimeters of spinal fluid. In case of vomiting or semiconsciousness interfering with swallowing, intravenous injections of the soluble sodium salt are indicated, or intramuscular injections, as recommended by Cable, who used the soluble salt of M. & B. 693 [33⅓ per cent solution]. Whether or not the soluble sodium salt can be safely injected intrathecally cannot be stated at the present time, but the injection of sulfanilamide by this route is indicated at the outset of treatment in order to secure effective concentrations in the spinal fluid as soon as possible.

TABLE 9.—*Pneumococcic Meningitis*

Authors	Compounds	Number of Patients	Percentage of Recoveries
Neal and Applebaum	Sulfanilamide	14	21
Allan, Mayer and Williams	Sulfanilamide	3	100
Hewell and Mitchell	Sulfanilamide	6	50
Finland and Brown	Sulfanilamide	10	60
Young	Sulfanilamide	1	Recovery
Cunningham	Soluble prontosil and sulfanilamide	1	Recovery
Mertins and Mertins	Soluble prontosil and sulfanilamide	1	Recovery
Latto	Soluble prontosil	1	Recovery
Barnett, Hartman, Perley and Ruhoff	Sulfapyridine	3	66
Robertson	Sulfapyridine	1	Recovery
Reid and Dyke	Sulfapyridine	1	Recovery
Cutts, Gregory and West	Sulfapyridine	1	Recovery
Cable	Sodium sulfapyridine	1	Recovery
McAlpine and Thomas	Sodium sulfapyridine	1	Recovery
MacKeith and Oppenheimer	Sodium sulfapyridine	5	40
Raman	Sodium sulfapyridine	1	Recovery
Hodes, Gimbel and Burnett	Sulfapyridine and sodium sulfapyridine	17	47

Peritonitis: In cases of primary pneumococcic peritonitis of infants and children, in which the mortality has varied from 65 to 100 per cent, Barnett and his colleagues have found sulfapyridine effective in the treatment of 3 patients, and Ladd and his colleagues have recorded the recovery of 2 of 3 patients treated with this compound and serum.

Gonococcic Infections.—While true infection of animals by gonococci is considered unattainable, Levaditi and Vaisman as well as Cohn and Peizer have observed favorable results in the treatment of experimental gonococcic peritonitis of mice with sulfanilamide; and an enthusiastic report by Dees and Colston on its use in the treatment of gonorrheal urethritis of men has been followed by a large number of

similar favorable reports (table 10), including the treatment of seminal vesiculitis, epididymitis, prostatitis, vulvovaginitis, endocervicitis and salpingitis.

Almost all observers, however, record 10 to 20 per cent of patients who fail to respond, probably owing to resistant strains of gonococci, and gonorrhea is a disease in which the criteria of cure are not readily amenable to exact statement. Lich and Rowntree have recently reported that the incidence of "cure" in a free clinic practice has been only 35 per cent, with recurrences in 11 per cent of 175 cases, the duration of symptoms averaging six and eight-tenths days and varying from one to more than thirty days.

TABLE 10.—*Gonococcic Urethritis*

Authors	Compounds	Number of Patients	Percentage "Cured"
Dees and Colston	Sulfanilamide	47	75
Mahoney	Sulfanilamide	205	85.4
Cokkinis and McElligott	Sulfanilamide	633	80
Silver and Elliott	Sulfanilamide	1,625	Effective
Reuter	Sulfanilamide	100	90
Herrold	Sulfanilamide	30	50
Grütz	Sulfanilamide	36	66
Crean	Sulfanilamide	100	90
Ferguson, Buckholtz and Gromet	Sulfanilamide	298	76
Keefer and Rantz	Sulfanilamide	63	100
Anwyl-Davies	Sulfanilamide	19	Unsatisfactory
Smith, Weil and Bird	Sulfanilamide	72	87.5
Walzak	Sulfanilamide	160	12.5
Orr	Sulfanilamide	134	87
Hoffman, Schneider, Blatt and Herrold	Sulfanilamide	25*	Effective
Lich and Rowntree	Sulfanilamide	175	35
McGregor-Robertson	Sulfapyridine	201	80 to 96
Lloyd	Sulfapyridine	106	85
Prebble	Sulfapyridine	65	48 to 62.5
Bowie, Anderson, Dawson and Mackay	Sulfapyridine	97	93
Batchelor, Lees, Murrell and Braine	Sulfapyridine	70	9 to 2.4
Marinkovitch	Sulfapyridine	50	86
Johnson, Leberman, Pepper and Lynch	Sulfapyridine	76	80.3

* Vulvovaginitis.

It is also clear that, depending on the method of treatment, a considerable number of patients may be placed in the dangerous state of being rendered symptom free or carriers of latent and residual infection. Practice in connection with irrigations and adjuvant measures varies widely, and the results to be expected in different forms of the disease are still in the process of being refined; certainly haphazard treatment is greatly to be deprecated, and the administration of adequate doses practically requires hospitalization for the best results. Furthermore, it is imperative for the laity to realize that sulfanilamide has no prophylactic value.

Some observers have expressed the opinion that treatment is more effective when begun after the acute stage is passed (Cokkinis and McElligott) and advise active immunization with vaccine for eight to ten

days before beginning treatment with the drug. The final answer to the treatment of gonorrhea in both sexes with sulfanilamide and sulfapyridine is therefore by no means solved; furthermore, with early subsidence of urethral discharge the cure and control of the disease become an increasingly formidable problem in relation to marriage and public health.

As shown in table 11, however, sulfanilamide and sulfapyridine have proved effective in the treatment of gonococcic ophthalmia and arthritis. Marvin and Wilkinson recorded the recovery of a patient

TABLE 11.—*Gonococcic Ophthalmia and Arthritis*

Authors	Disease	Compounds	Number of Patients	Results
Michie	Ophthalmia	Sulfapyridine	2	Effective
Willis	Ophthalmia	Sulfanilamide	4	Effective
Barbour and Towsley	Ophthalmia	Sulfanilamide	15	Effective
Michels	Ophthalmia	Sulfanilamide	15	Effective
Fernandez and Fernandez	Ophthalmia	Sulfanilamide	8	Effective
Brulé, Hillemand and Vilde	Arthritis	Sulfanilamide	3	Effective in 2
Keefer and Rantz	Arthritis	Sulfanilamide	14	Effective

TABLE 12.—*Sulfanilylsulfanilamide and Sulfanilyldimethylsulfanilamide in the Treatment of Gonococcic Urethritis*

Authors	Compounds	Number of Patients	Percentage "Cured"
Mergelsberg and Grümer	Uleron*	69	77
Gennerich	Uleron*	64	100
Fuhs and Volavsek	Uleron*	169	94
Wilkie	Uleron*	100	74
Walzak	Disulon†	36	19.4
Walzak	Disulon†	160‡	12.5
O'Crowley, James and Sutton	Disulon†	85	94
Shelley	Disulon†	100	97

* Sulfanilyldimethylsulfanilamide.
† Sulfanilylsulfanilamide.
‡ Treated with sulfanilamide.

with gonococcic meningitis but were not inclined to give sulfanilamide the credit. In 22 cases recorded in the literature in which sulfanilamide was not administered, the mortality was 45 per cent.

While neoprontosil appears to be less effective than sulfanilamide in gonorrhea, sulfanilylsulfanilamide and sulfanilyldimethylsulfanilamide are regarded by the German physicians as superior. I have not attempted to review the extensive literature (more than 160 articles alone since 1938) but have included some of the more recent reports in table 12. It is generally recommended to delay treatment for about three weeks in order to allow the mobilization of body defenses, but it appears that the results are not superior to those observed with sulfanilamide; furthermore, these compounds are much more likely to produce

peripheral neuritis. In a few cases renal or even hepatic injury has been reported as following excessive dosage or a prolonged period of administration, although it is stated that nausea, vomiting, dizziness and cyanosis are less frequently observed than with the use of sulfanilamide.

Infections of the Urinary Tract.—The prontosils have been used in Germany for the treatment of Bacillus coli and staphylococcic infections of the urinary tract of both adults and children, with uniform success, but there seems to be no reason for believing them to be superior or even perhaps equal to sulfanilamide for this purpose (table 13).

These compounds have been found much more bactericidal in alkaline than in acid urine. As shown by Helmholtz, sulfanilamide and mandelic acid complement one another and have separate indications.

TABLE 13.—*Infections of the Urinary Tract*

Authors	Compounds	Patients		Results
		Number	Kind	
Pernice	Original prontosil	18	Children	Effective
Maraun	Original prontosil	38	Children	87 per cent cured
Meissner	Soluble prontosil	8	Adults	Effective
Clark	Sulfanilamide	Not stated	Adults	Effective
Helmholtz	Sulfanilamide	Not stated	Children	Effective
Kenny, Johnston and von Haebler	Sulfanilamide	46	Women	Effective
Cuthbert	Sulfanilamide	79	Women	Effective
Gaudin, Zide and Thompson	Sulfanilamide	100	Men	Not recommended*
Herrold	Sulfanilamide	16	Adults	75 per cent cured
Melton and Beck	Sulfapyridine	71	Adults	78 per cent cured

* After transurethral prostatectomy.

The former can be given in the acute stage, acts best in alkaline urine, is effective even in the presence of renal damage, is effective in Bacillus proteus infection and is superior in the treatment of coexisting prostatitis, in some cases of which it has been demonstrated in the secretions; but it fails against Str. faecalis, and about 15 per cent of patients cannot take it in sufficient dosage. Mandelic acid requires highly acid urine and good renal function and is effective against Str. faecalis. Furthermore, mandelic acid is prefererd when applicable since it is safer. In other words, neoprontosil, sulfanilamide and sulfapyridine have been generally found highly effective against infections of the urinary tract due to B. coli, Bacillus proteus, hemolytic streptococci and some staphylococci, but they are less effective in infections due to Str. faecalis. Albright, Dienes and Sulkowitch have found sulfanilamide ineffective in 2 cases of pyelonephritis with nephrocalcinosis due to Haemophilus influenzae. In this connection it must be emphasized, however, that strains of B. coli vary in susceptibility to sulfanilamide and that failure

in treatment may be due to infection with a strain unusually resistant both in vitro and in vivo as reported by Kolmer and Rule in 1939. This is also true of infections due to staphylococci, and under such circumstances an in vitro test for susceptibility to the compound may be of assistance in arranging dosage. Probably intravenous injection of 0.2 Gm. of neoarsphenamine twice weekly is to be preferred in the treatment of infections with unusually resistant staphylococci as, curiously, the compound is highly effective under these conditions.

Staphylococcic Infections.—As previously stated, the first published report on the therapeutic use of the original prontosil was that by Foerster of the treatment of a child with staphylococcic septicemia. In fact, Domagk found this compound somewhat effective against

TABLE 14.—*Experimental Staphylococcic Infections*

Author	Compound	Animal	Treated		Controls	
			Number	Percentage of Survivors	Number	Percentage of Survivors
Buttle	Sulfanilamide	Mice	30	50	10	0
Mellon, Shinn and McBroom	Sulfanilamide	Mice	21	38	31	14
Feinstone, Bliss, Ott and Long	Sulfanilamide	Mice	50	34	50	10
Whitby	Sulfapyridine	Mice	40	15	18	16
Whitby	Sulfapyridine	Mice	80	7.5	..	..
Bliss and Long	Sulfanilamide	Mice	50	8	30	0
Bliss and Long	Sulfapyridine	Mice	49	33	..	..
Barlow and Homburger	Sulfathiazole*	Mice	20	70	20	0
Barlow and Homburger	Sulfamethylthiazole†	Mice	20	90	..	..
Barlow and Homburger	Sulfaphenylthiazole†	Mice	20	45	..	..
Barlow and Homburger	Sulfapyridine	Mice	20	30	..	..

* 2-(paraaminobenzenesulfonamido)-thiazole.
† 2-(paraaminobenzenesulfonamido)-methylthiazole.

experimental staphylococcic infections, and it is astonishing that since then so few clinical results have been published. I surmise, however, that this is not because both the prontosils, sulfanilamide and sulfapyridine, have failed to be employed but because the results have been so poor (especially in staphylococcic septicemia) and because failures are so seldom reported.

As shown in table 14, sulfanilamide and sulfapyridine, however, are not without some effect in the treatment of experimental staphylococcic infections of mice, and Domagk in 1937 stated that better results have been observed with uliron (sulfanilyldimethylsulfanilamide). Barlow and Homburger have found sulfamethylthiazol (2-sulfanilamidomethylthiazole; 2-[paraaminobenzene sulfonamido]-methylthiazole), a thiazole analogue of sulfapyridine prepared by Fosbinder and Walter, more effective than sulfapyridine; and this compound, as well as sulfathiazole (2-sulfanilamidothiazole; 2-[paraaminobenzene-

sulfonamido]-thiazole), is commanding special attention at present in the treatment of staphylococcic septicemia, although it is too early to express an opinion of their clinical value. These compounds (Winthrop Chemical Company) are given in doses of 5 Gm. (10 tablets), followed by 1.5 Gm. every four hours, day and night, for two or three days, at which time each dose may be decreased and the time interval between doses lengthened in conformity with the condition of the patient. Their toxicity is low, as recently reported by Van Dyke and his colleagues.

Comparatively few successes have been reported in the treatment of staphylococcic septicemia of human beings with the prontosils, sulfanilamide and sulfapyridine (table 15); and while the literature records many failures, it is a safe assumption that a large number of such have not been recorded. At the present time sulfamethylthiazol and sulfapyridine appear to be the remedies of choice, although the

TABLE 15.—*Staphylococcic Septicemia*

Authors	Compounds	Number of Patients	Results
Foerster	Original prontosil	1	Recovery
Colebrook and Kenny	Sulfanilamide	5*	Two recoveries
O'Brien and McCarthy	Sulfapyridine	1	Recovery
Fenton and Hodgkiss	Sulfapyridine	1	Recovery
Wade	Sulfapyridine	1	Recovery
Abramson and Flacks	Soluble prontosil, uleronf and sulfapyridine	6	Two recoveries
Galewsk†	Sulfapyridine	1	Recovery
Mendell	Sulfanilamide	3	No recoveries
Thornhill, Swart and Reel	Sulfanilamide	2	Recovery

* Puerperal septicemia.
† Sulfanilyldimethylsulfanilamide.

chemotherapy of severe staphylococcic infections is by no means as satisfactory as that of infections due to hemolytic streptococci.

Bloch and Pacella have recorded a recovery of a patient with staphylococcic meningitis credited to sulfanilamide therapy.

Undulant Fever.—It is difficult to assess the value of sulfanilamide and its derivatives in the treatment of brucellosis, because primary favorable effects may not be an index of cure in the sense of complete eradication of infection.

Comparatively little has been reported on the therapeutic activity of these compounds in the treatment of experimental brucellosis of the lower animals. Welch, Wentworth and Mickle found that the oral administration of sulfanilamide markedly increased the opsonocytophagic activity of the serums of guinea pigs infected with Brucella abortus. Chinn observed that the oral administration of sulfanilamide to guinea pigs was effective in preventing generalized infections with Br. abortus, since cultures of the livers and spleens of treated animals subjected to

autopsy after the expiration of treatment were sterile in the majority of instances. In the guinea pigs inoculated intra-abdominally with Br. abortus, Brucella melitensis and Brucella suis it was thought that complete cures were obtained in 50 to 100 per cent, the compound being less effective against Br. melitensis and Br. suis than against Br. abortus. Similar results have been reported by Menefee and Poston with guinea pigs inoculated intra-abdominally with Br. abortus and treated with sulfanilamide by oral administration.

TABLE 16.—*Experimental Brucellosis of Mice*

Compounds	Brucella Abortus		Brucella Melitensis		Brucella Suis	
	Number of Mice	Percentage of Survivors	Number of Mice	Percentage of Survivors	Number of Mice	Percentage of Survivors
Sulfanilamide	32	37.5	32	None	16	None
Neoprontosil	32	31.2	32	25	16	None
Sulfapyridine	32	31.2	32	37.5	16	None
Dagenan*	32	25	32	25	16	None
Aldanil †	32	56.2	32	6.2	16	None
Untreated controls	32	6.2	32	None	16	None

* Sodium sulfapyridine (Merck & Co. Inc.).
† Sodium formaldehyde sulfoxylate derivative of sulfanilamide (Abbott Laboratories).

TABLE 17.—*Undulant Fever*

Authors	Compounds	Number of Patients	Results
Newman	Soluble prontosil	16	Favorable
Dalyrymple-Champneys	Sulfanilamide	27	24 benefited
Welch, Wentworth and Mickle	Sulfanilamide	5	Favorable
Bynum	Sulfanilamide	6	Unsatisfactory
Richardson	Soluble prontosil	2	Favorable
Francis	Soluble prontosil	2	Favorable
Punch	Soluble prontosil	1	Favorable
Toone and Jenkins	Sulfanilamide	1	Favorable
Stern and Blake	Sulfanilamide	3	Favorable
Traut and Logan	Sulfanilamide	2	Favorable
Long and Bliss	Sulfanilamide	5	Unfavorable in 4

Kolmer and Rule have used mice inoculated intra-abdominally with virulent strains of Br. abortus, Br. melitensis and Br. suis, with the results shown in table 16. All five of the compounds employed gave best therapeutic results in the 160 mice infected with Br. abortus. Among the 160 infected with Br. melitenisis, the compounds were much less effective; while in the 80 infected with Br. suis the therapeutic effects were nil in so far as survival was concerned, although all the compounds appreciably prolonged the lives of the mice, especially sulfanilamide and sulfapyridine.

As shown in table 17, the majority of clinical reports on the treatment of undulant fever in human beings have been favorable, although I believe that these refer more to the primary effects, such as the relief

of fever and symptoms during the acute early stage, than to complete or biologic cure, since recurrences have frequently followed cessation of treatment. My own experience has been confined to 3 patients, in 2 of whom the condition was due to Br. abortus and in 1, to Br. melitensis (a laboratory infection). The former 2 were treated with neoprontosil, with complete recoveries, in so far as I can judge over one to three years of follow-up observation; the infection due to Br. melitensis was at first refractory to sulfanilamide, neoprontosil and sulfapyridine but finally yielded satisfactorily to sulfanilamide, which I believe is the compound of choice. Certainly clinical experience has taught that the primary beneficial results are not acceptable as "cure," since relapses may occur; and for this reason I advise continuing the administration of sulfanilamide in decreasing doses for at least two months after the subsidence of fever and symptoms. Only a few cases of endocarditis due to brucellosis have been recorded, but 1 in which sulfanilamide was administered by Smith and Curtis ended in failure.

TABLE 18.—*Chancroid (Haemophilus of Ducrey)*

Author	Compound	Number of Patients	Results
Hutchison	Sulfanilamide	11	Favorable
Hanschell	Sulfanilamide	20	Favorable
Kornblith, Jacoby and Wishengrad	Sulfanilamide	120	Favorable
Greenblatt and Sanderson	Sulfanilamide	5	Favorable

Chancroid.—While I have no knowledge of the use of sulfanilamide in the treatment of experimental infections due to Haemophilus ducreyi, as shown in table 18, this compound has apparently proved highly effective in the treatment of chancroid and appears to be the method of choice along with local measures, since all drugs hitherto employed have proved ineffective in the management of this tedious disease which has no mortality and causes no chronic invalidism but is of high nuisance rank. Appleyard has informed me that he has observed excellent results from local applications of powdered sulfanilamide, which is interesting in relation to the effects of the compound by local applications, shortly to be discussed with more detail. Fagerstrom has also found sulfanilamide effective in the treatment of ulcerative and gangrenous balanitis.

Typhoid Fever.—On the basis of results observed in the treatment of experimental Bacillus typhosus infections of mice (table 19), one would expect that neoprontosil, sulfanilamide and sulfapyridine might show a favorable therapeutic response in typhoid fever. But so far clinical data are too scanty to permit the expression of an opinion. According to Harries, Swyer and Thompson, sulfapyridine has an effect

on the bacteremia and fever of the disease and in general is to be regarded as of some value in treatment, but aside from these effects the evidence in favor of these compounds in treatment is still far from being convincing, although apparently worthy of further trial. Barer recorded success with the soluble prontosil in the treatment of post-typhoid urinary infection, but I can find no data bearing on the use of this and allied compounds in the treatment of typhoid carriers.

Clostridium Welchii Infections.—In 1937 Domagk found uleron (sulfanilyldimethylsulfanilamide) sulfanilylsulfanamide and sulfanilamide somewhat effective in the treatment of mice and guinea pigs inoculated with Clostridium welchii. As shown in table 20, Long and Bliss have found sulfanilamide and sulfapyridine highly effective in these experi-

TABLE 19.—*Experimental Typhoid Infection and Typhoid Fever*

Authors	Compounds	Subject	Treated		Controls	
			Number	Results	Number	Results
Buttle, Parish, McLeod and Stephenson	Soluble prontosil	Mice	30	83% survived	20	30% survived
Kolmer and Rule.....	Sulfanilamide	Mice	22	14% survived	8	0 survived
Kolmer and Rule.....	Sulfapyridine	Mice	10	10% survived	4	0 survived
Schmidt.....	Soluble prontosil	Human beings	3	Favorable		
Diefenbach and Yuskis.....	Sulfanilamide	Human beings	1	Favorable		
Harkelroad.....	Sulfanilamide	Human beings	1	Favorable		
Coxon.....	Sulfapyridine	Human beings	1	Unfavorable		
Harries, Swyer and Thompson	Soluble prontosil and sulfapyridine	Human beings	7	Favorable		

mental infections. Since then the clinical results reported by Bohlman in the treatment of 3 patients in whom gas gangrene developed in spite of prophylactic antitoxin were so impressive, along with the reports of Baker and of Sadusk and Manahan in the treatment of postabortal and puerperal infections with septicemia, as to leave no doubt but that sulfanilamide and sulfapyridine are valuable adjuncts to antitoxin in the treatment of these dangerous infections.

Tuberculosis.—As reported by Allison and Myers, sulfapyridine was ineffective in the treatment of 7 patients with active pulmonary tuberculosis, although it is likely that this compound, as well as neoprontosil and sulfanilamide, may be helpful in combating secondary infection of open lesions, especially infections due to hemolytic streptococci and Staph. aureus, as indicated by the report of Weidekamp on tuberculous disease of the bone. Sappington and Favorite have found neoprontosil

and sulfanilamide ineffective in the treatment of 3 patients with tuberculous meningitis.

Furthermore, the results of treatment of experimental tuberculous infections of guinea pigs and rabbits with both human and bovine strains

TABLE 20.—*Clostridium Welchii Infections*

Authors	Compounds	Animal	Treated		Controls	
			Number	Percentage of Survivors	Number	Percentage of Survivors
Long and Bliss	Sulfanilamide	Guinea pigs	64	44	41	5
Bliss, Feinstone, Garrett and Long	Sulfanilamide	Mice	40	32	40	7
Bliss, Feinstone, Garrett and Long	Sulfapyridine	Mice	40	40		
Bohlman	Sulfanilamide	Human beings	3	Recovered		
Baker	Sulfapyridine	Human beings*	1	Recovered		
Sadusk and Manahan	Sulfanilamide	Human beings†	2	Recovered		

* Septicemia and peritonitis.
† Postabortal.

TABLE 21.—*Experimental Tuberculosis*

Authors	Compounds	Animals	Treated	
			Number	Results
Rich and Follis	Sulfanilamide	Guinea pigs	31	Slightly effective
Greey, Campbell and Culley	Sulfanilamide	Guinea pigs	76	Slightly effective
Greey, Campbell and Culley	Sulfanilamide	Rabbits	10	No effect
Smithburn	Sulfanilamide	Guinea pigs	10	No effect
Kolmer, Raiziss and Rule	Sulfanilamide	Guinea pigs	30	No effect
Steinbach and Dillon	Sulfanilamide	Guinea pigs	66	No effect
Buttle and Parish	Sulfanilamide	Guinea pigs	40	Slightly effective*
Ballon and Guernon	Sulfanilamide	Guinea pigs	38	Slightly effective
Dietrich	Soluble prontosil	Guinea pigs	20	No effect
Feldman and Hinshaw	Sulfapyridine	Guinea pigs	40	Definitely effective

* With human strain; little effect in guinea pigs and none in rabbits with a bovine strain.

of Mycobacterium tuberculosis leave one with the impression that little or nothing is to be expected in the treatment of human tuberculosis in so far as an effect on the tubercle bacillus itself is concerned, since only massive doses at best have shown inhibitory effects on experimental infections (table 21).

Miscellaneous Bacterial Diseases.—As previously stated, neoprontosil and sulfanilamide have proved effective in the treatment of a high

percentage of infections of the urinary tract due to B. coli and B. proteus and these compounds as well as sulfapyridine have been found effective in the treatment of experimental infections in mice (table 22). All three have also been successfully employed in the treatment of B. coli septicemia and are far superior to any other chemical agent in the

TABLE 22.—*Miscellaneous Experimental Bacterial Infections*

				Treated		Controls	
Authors	Compounds	Infection	Animal	Number	Percentage of Survivors	Number	Percentage of Survivors
Cooper, Gross and Lewis	Sulfanilamide	Bacillus coli	Mice	40	55	..	..
Cooper, Gross and Lewis	Sulfapyridine	Bacillus coli	Mice	10	80	..	..
Cooper, Gross and Lewis	Sulfanilamide	Bacillus proteus	Mice	10	80	..	..
Cooper, Gross and Lewis	Sulfapyridine	Bacillus proteus	Mice	10	90	..	..
Kolmer and Rule.....	Sulfanilamide	Bacillus dysenteriae	Mice	13	0	5	0
Buttle, Parish, McLeod and Stephenson	Sulfanilamide	Bacillus friedländer	Mice	70	17	40	0
Bliss, Feinstone, Garrett and Long	Sulfanilamide	Bacillus friedländer	Mice	45	0	30	0
Bliss, Feinstone, Garrett and Long	Sulfapyridine	Bacillus friedländer	Mice	45	0	..	..
Kolmer and Rule.....	Sulfanilamide	Bacillus friedländer	Mice	32	7	8	0
Kolmer and Rule.....	Sulfapyridine	Bacillus friedländer	Mice	16	25	4	0
Cooper, Gross and Lewis	Sulfanilamide	Bacillus pyocyaneus	Mice	40	53	..	..
Cooper, Gross and Lewis	Sulfapyridine	Bacillus pyocyaneus	Mice	20	50	..	..
Schütze.....	Sulfapyridine	Bacillus pestis	Mice and rats	42	76	42	5
Cooper, Gross and Lewis	Sulfanilamide	Bacillus pertussis	Mice	60	0	20	0
Cruickshank.....	Sulfanilamide and sulfapyridine	Bacillus anthracis	Mice	120	0	30	0
May and Buck.....	Sulfapyridine	Bacillus anthracis	Mice	24	8.3	24	4.1
Campbell.....	Sulfapyridine	Spirochaeta pallida	Rabbits	7	No effect	..	..
Porter and Hale.....	Sulfanilamide	Listerella monocytogenes	Mice	60	60	60	5
Porter and Hale.....	Sulfapyridine	Listerella monocytogenes	Mice	20	40	20	0
Porter and Hale.....	Sulfanilamide	Erysipelothrix	Mice	40	0	110	6
Porter and Hale.....	Sulfapyridine	Erysipelothrix	Mice	70	1.4	..	..

treatment of this dangerous infection. My own experience has been with 5 patients with positive blood cultures, 4 of whom recovered.

On the other hand, sulfanilamide is apparently ineffective in the treatment of experimental infections of mice due to Bacillus dysenteriae, and reports on its effectiveness in the treatment of bacillary dysentery lack confirmation at the present time.

Sulfanilamide and especially sulfapyridine are slightly effective in the treatment of infections of mice due to Friedländer's bacillus, but

clinical reports are too few to justify an opinion of their clinical value. I have had 1 case of meningitis due to Friedländer's bacillus, secondary to suppurative ethmoiditis, in which temporary improvement was observed under treatment with sulfapyridine but the disease was fatal. A few encouraging reports have been made on the successful use of sulfapyridine in the treatment of the highly mortal pneumonia due to Fried-

TABLE 23.—*Miscellaneous Bacterial Diseases*

Authors	Compounds	Disease	No. of Patients	Results
Basman and Perley	Sulfanilamide	Bacillus proteus meningitis	1	Recovered
Stewart and Bates	Sulfanilamide	Bacillus pyocyaneus (intestinal)	1	Recovered
Banks	Sulfanilamide	Bacillus pyocyaneus (intestinal)	1	Recovered
Thompson and Greenfield	Sulfanilamide	Pertussis	Not stated	Some value*
Neal and Applebaum	Sulfanilamide	Influenzal meningitis	1	Recovered
Eley	Sulfapyridine	Influenzal meningitis	2	Recovered
Roche and Caughey	Sulfapyridine	Influenzal meningitis	2	Recovered
Hamilton and Neff	Sulfapyridine	Influenzal meningitis	1	Recovered
Sappington and Favorite	Sulfanilamide	Influenzal meningitis	2	Ineffective
Meyer and Amtman	Sulfapyridine	Bacillus friedländer septicemia	1	Recovered
Swift, Moen and Hirst	Sulfanilamide	Rheumatic fever	8	Doubtful
Thomas and France	Sulfanilamide	Rheumatic fever	Few	Encouraging
Massell and Jones	Sulfanilamide	Rheumatic fever	58 (7 with chorea)	Ineffective
Coburn and Moore	Sulfanilamide	Rheumatic fever	Not stated	Some value*
Curtis	Sulfanilamide	Tularemia	1	Effective
Stannus and Findlay	Sulfapyridine	Glandular fever	1	Effective
Strickler and Stone	Sulfanilamide	Pyogenic dermatoses	12	Some value
Wilson	Sulfanilamide	Lupus erythematosus	1	Ineffective
Engels	Sulfanilamide	Lupus erythematosus	1	Ineffective
Walker	Sulfanilamide	Actinomysosis	1	Effective
Miller and Fell	Sulfanilamide	Actinomycosis	1	Effective
Poulton	Sulfanilamide	Actinomycosis	1	Effective

* In the prevention of complications.

länder's bacillus; my personal experience has been with 3 patients with positive blood cultures. Of these, 2 recovered under intensive treatment with this compound, which I believe at present may be the compound of choice.

Cooper and his associates found that sulfanilamide had no therapeutic value in the treatment of experimental Bacillus pertussis infections of mice and this is likewise apparently true of pertussis of children except that this compound, as well as neoprontosil and sulfapyridine, may have some value in the prevention of the dreaded bronchopneumonia and other complications of this disease (table 23).

On the other hand, sulfanilamide and sulfapyridine have apparently proved effective in the treatment of some patients with the highly mortal Bacillus influenzae meningitis, especially when treatment includes the administration of adequate amounts of immune serum. I have had 3 patients, with 1 recovery, who were treated with maximum doses of neoprontosil by parenteral administration, combined with intravenous and intrathecal injections of serum.

Sulfanilamide has also proved somewhat effective in the treatment of experimental B. pyocyaneus infections of mice, and while clinical reports are too few to warrant an expression of its clinical value, this compound, as well as neoprontosil, appears worthy of trial in the treatment of severe infections, especially septicemia. I have had 1 patient, a child, who had septicemia with positive blood cultures but who recovered after the oral and parenteral administration of neoprontosil.

The results in acute rheumatic fever are doubtful, although it is thought that sulfanilamide may reduce or prevent the incidence of recurrence of this disease, and its administration may be worth while for this purpose.

Encouraging reports have also been made on the effectiveness of sulfanilamide in the treatment of patients with tularemia, lupus erythematosus and glandular fever. It has proved ineffective in experimental syphilis of rabbits, and Pariser has found prontylin (sulfanilamide) to exert but little effect on the reactions of the blood in seroresistant forms of this disease. Some fungi are susceptible in vitro, but among mycotic diseases sulfanilamide has apparently proved encouraging and effective only in patients with actinomycosis, results indicating that it is probably worthy of trial in the treatment of this chronic disease.

Virus Diseases.—As shown in table 24, the only experimental virus disease in which sulfanilamide and sulfapyridine have definitely proved effective is lymphogranuloma venereum in mice. As shown in table 25, these compounds have also proved highly effective in the treatment of the disease in human beings.

The curative effects of these compounds in experimental lymphocytic choriomeningitis are still doubtful, and apparently clinical reports are not available, although the tendency to spontaneous recovery renders chemotherapy hardly worth while.

In experimental encephalitis due to the St. Louis virus as well as in that due to herpetic virus and to the virus of equine encephalomyelitis, sulfanilamide has proved ineffective, and there is no reason for expecting better clinical results.

Sulfanilamide may possess some therapeutic power in experimental infections of mice with the virus of influenza, but it is doubtful if this compound, or neoprontosil or sulfapyridine, has any helpful effects in

TABLE 24.—*Experimental Virus and Rickettsial Infections*

Authors	Compounds	Infection	Animals	Results
MacCallum and Findlay	Sulfanilamide	Lymphogranuloma venereum	Mice	Effective
Bär	Sulfanilamide	Lymphogranuloma venereum	Mice	Effective
Levaditi	Sulfanilamide	Lymphogranuloma venereum	Mice	Effective
McKee, Rake, Greep and Van Dyke	Sulfapyridine	Lymphogranuloma venereum	Mice	Effective
McKee, Rake, Greep and Van Dyke	Sulfathiazole*	Lymphogranuloma venereum	Mice	Effective
Rosenthal	Soluble prontosil	Choriomeningitis	Mice	Effective
McKinley, Meek and Acree	Sulfanilamide	Choriomeningitis	Mice	Ineffective
McKinley, Meek and Acree	Sulfanilamide	St. Louis encephalitis	Monkeys and mice	Ineffective
McKinley, Meek and Acree	Sulfanilamide	Herpetic encephalitis	Monkeys and mice	Ineffective
McKinley, Meek and Acree	Sulfanilamide	Poliomyelitis	Monkeys	Ineffective
Kelson	Sulfanilamide	Poliomyelitis	Monkeys	Ineffective
Toomey and Takacs	Sulfanilamide and sulfapyridine	Poliomyelitis	Monkeys	Ineffective
Climenko, Crossley and Northey	Sulfanilamide	Influenza	Mice	Ineffective
Pittman	Sulfapyridine	Influenza	Mice	Effective
Cooper, Gross and Lewis	Sulfanilamide	Rabies	Rats	Slightly effective
Dochez and Slanetz	Sodium sulfanilamide	Canine distemper	Ferrets, dogs and cats	Doubtful
Dickerson and Whitney	Sulfanilamide	Canine distemper	Dogs	Ineffective
Topping	Neoprontosil and sulfapyridine	Rocky Mountain spotted fever and endemic typhus fever	Guinea pigs	Ineffective

* 2-(paraaminobenzenesulfonamido)-thiazole.

TABLE 25.—*Virus Diseases*

Authors	Compounds	Diseases	Number of Patients	Results
Shaffer and Arnold	Sulfanilamide	Lymphogranuloma venereum	12	Favorable
Knight and David	Sulfanilamide	Lymphogranuloma venereum	2	Favorable
Earle	Sulfapyridine	Lymphogranuloma venereum	14	Favorable
Hebb, Sullivan and Felton	Sodium sulfanilylsulfanilate and sodium sulfanilate	Lymphogranuloma venereum	14	Favorable
Shropshear	Sulfanilamide	Lymphogranuloma venereum	10	Favorable
Young and Moore	Sulfanilamide	Influenza	5	Effective*
Thompson and Greenfield	Sulfanilamide	Measles and pertussis	Not stated	Effective*
Vigors	Sulfanilamide	Trachoma	2	Effective
Kirk, McKelvie and Russell	Sulfanilamide	Trachoma	25	Effective
Loe	Sulfanilamide	Trachoma	140	Effective
Harley, Brown and Herrell	Sulfanilamide and neoprontosil	Trachoma	11	Effective
Spearman and Vandevere	Sulfapyridine	Trachoma	2	Effective
Larimer and Wiesser	Sulfanilamide	Human equine encephalitis	16	Ineffective

* In the prevention of bacterial complications.

the treatment of this disease in human beings except, possibly, to reduce the incidence of complications due to secondary bacterial infection, especially with hemolytic streptococci. The same is true of the virus of measles.

Patients with trachoma, however, which is now widely regarded as a virus disease, are being successfully treated with sulfanilamide, sulfapyridine and neoprontosil. The literature records the treatment of over 300 patients with these compounds, with excellent results, especially in the early stages of the disease.

Unfortunately, the compounds have proved completely ineffective in the prophylaxis and treatment of experimental acute anterior poliomyelitis of monkeys. Rule and I have administered neoprontosil, sulfanilamide and sulfapyridine to 6 monkeys (2 for each compound) by the oral route in doses as high as 0.1 Gm. per kilogram of body weight every twelve hours for seven days in succession (first dose immediately after intracerebral inoculation), without the slightest effect, since flaccid paralysis developed in all, including 2 controls, in from seven to eleven days after inoculation. While Wagner stated the belief that sulfapyridine is worthy of clinical trial in the treatment of the disease, it is unlikely that helpful effects will be subsequently observed.

Caro has reported encouraging results in the treatment of the dreadful pemphigus with sulfanilamide, but to the best of my knowledge this compound has not generally proved effective, although Troup and White have recently reported the successful treatment of a patient with pemphigus neonatorum with sulfapyridine, and Erskine and Royds reported the use of the same compound in an adult with pemphigus vulgaris in whom agranulocytosis developed from the drug; the patient recovered. While the etiology is uncertain, I personally suspect that the disease is due to a virus. My experience is confined to 2 patients treated with sulfapyridine, who ultimately succumbed. It was my impression, however, that the compound reduced the degree and severity of secondary infection of the blisters with staphylococci and streptococci.

However, I have had excellent results with sulfapyridine in the treatment of 2 patients with dermatitis herpetiformis, which I also suspect may be a virus disease. After arsenic and all other measures failed, both patients promptly responded to the oral administration of the compound. At the time of writing both are kept free of the lesions by taking 10 to 20 grains (0.65 to 1.29 Gm.) per day in divided doses, but as soon as medication stops the lesions return with intolerable itching. It is my hope, however, that they will ultimately recover after prolonged treatment, as the condition in each case is chronic and of three and seven years' duration, respectively.

Recently McCammon has reported that the treatment of 4 patients with smallpox with sulfanilamide gave favorable results. Whether or

not the compound is therapeutically effective against the virus cannot be stated, as the improvement noted may have been due to the prevention of secondary streptococcic and staphylococcic infection of the lesions by this drug.

McKinley, Meck and Acree have found sulfanilamide ineffective in the treatment of fibromatosis and myxomatosis of rabbits, which may be due to viruses.

Diseases Due to Animal Parasites.—The only parasitic disease that I know of in which neoprontosil, sulfanilamide and sulfapyridine may be effective is malaria, especially in monkeys infected experimentally

TABLE 26.—*Diseases Due to Animal Parasites*

Authors	Compounds	Diseases	Animals	Results
Coggeshall	Sulfanilamide	Malaria	Monkeys, canaries and chicks	Effective*
Pakenham-Walsh and Rennie	Sulfanilamide and sulfapyridine	Malaria	Human beings	Effective
Diaz deLeon	Soluble prontosil	Malaria	Human beings	Effective
Hill and Goodwin	Soluble prontosil	Malaria	Human beings	Effective
Hall	Soluble prontosil and sulfanilamide	Malaria	Human beings	Ineffective
Faget, Palmer and Sherwood	Sulfanilamide	Malaria	Human beings	Ineffective
McCoy	Sulfanilamide	Trichinosis	Human beings	Ineffective
McNaught, Beard and De Eds	Sulfanilamide	Trichinosis	Rats	Slightly effective†
Brown	Sulfanilamide	Filariasis	Dogs	Ineffective
Kolmer and Rule	Sulfanilamide	Trypanosomiasis	Rats	Ineffective

* Rhesus monkeys inoculated with Plasmodium knowlsi; ineffective against Plasmodium inui, Plasmodium cathemerium and Plasmodium lophurae.
† In reducing the number of encysting trichinellas by 55 per cent.

with Plasmodium knowlsi and in human beings infected with Plasmodium vivax (table 26). Coggeshall has found that with mixed malarial infections in the same experimental animal sulfanilamide eradicates a virulent P. knowlsi infection, leaving the animal with a milder chronic Plasmodium inui infection. However, sulfanilamide is an inferior therapeutic agent in human malaria. Pakenham-Walsh and Rennie found sulfapyridine destructive to P. vivax in a patient with dementia paralytica inoculated with this parasite, and they advised against its administration during the malarial treatment of this disease.

Otherwise these compounds appear to be ineffective in the treatment of patients with trichinosis, filiariasis and trypanosomiasis and most likely also with the different types of leishmaniasis.

TABLE 27.—*Summary of Therapeutic Effectiveness in the Treatment of Experimental Infections*

Infections	Animals	Compounds	Results
Hemolytic streptococcus	Mice and rabbits	The prontosils, sulfanilamide and sulfapyridine	Effective
Meningococcus	Mice	Sulfanilamide, sulfapyridine and sulfathiazole*	Effective
Pneumococcus (all types)	Mice, rabbits, rats and dogs	Sulfanilamide, sulfapyridine and sulfathiazole	Effective
Gonococcus	Mice	Sulfanilamide	Effective
Staphylococcus	Mice	Sulfanilamide, sulfapyridine and sulfamethylthiazole†	Fairly effective
Brucella	Guinea pigs and mice	Neoprontosil, sulfanilamide and sulfapyridine	Effective
Bacillus typhosus	Mice	Neoprontosil, sulfanilamide and sulfapyridine	Fairly effective
Clostridium welchii	Guinea pigs and mice	Sulfanilamide and sulfapyridine	Effective
Bacillus tuberculosis	Guinea pigs and rabbits	Sulfanilamide and sulfapyridine	Doubtfully effective
Bacillus coli	Mice	Sulfanilamide and sulfapyridine	Effective
Bacillus proteus	Mice	Sulfanilamide and sulfapyridine	Effective
Bacillus dysenteriae	Mice	Sulfanilamide and sulfapyridine	Ineffective
Bacillus friedländer	Mice	Sulfanilamide and sulfapyridine	Slightly effective
Bacillus pyocyaneus	Mice	Sulfanilamide and sulfapyridine	Effective
Bacillus pertussis	Mice	Sulfanilamide	Ineffective
Bacillus pestis	Mice and rats	Sulfapyridine	Effective
Bacillus anthracis	Mice	Sulfanilamide and sulfapyridine	Doubtfully effective
Spirochaeta pallida	Rabbits	Sulfapyridine	Ineffective
Listerella monocytogenes	Mice	Sulfanilamide and sulfapyridine	Effective
Erysipelothrix	Mice	Sulfanilamide and sulfapyridine	Ineffective
Virus of lymphogranuloma venereum	Mice	Sulfanilamide, sulfapyridine and sulfathiazole*	Effective
Virus of choriomeningitis	Mice	Neoprontosil	Doubtfully effective
Virus of encephalitis	Mice and monkeys	Sulfanilamide	Ineffective
Virus of poliomyelitis	Monkeys	Sulfanilamide and sulfapyridine	Ineffective
Virus of influenza	Mice	Sulfanilamide and sulfapyridine	Ineffective
Virus of rabies	Rats	Sulfanilamide	Ineffective
Rickettsia	Guinea pigs	Neoprontosil and sulfapyridine	Ineffective
Malaria	Monkeys	Sulfanilamide and sulfapyridine	Slightly effective
Trichinosis	Rats	Sulfanilamide	Doubtfully effective
Filariasis	Dogs	Sulfanilamide	Ineffective
Trypanosomiasis	Rats	Sulfanilamide	Ineffective

* 2-(paraaminobenzenesulfonamido)-thiazole.
† 2-(paraaminobenzenesulfonamido)-methylthiazole.

Summary.—In table 27 I have attempted to summarize the therapeutic effectiveness of the prontosils, sulfanilamide and sulfapyridine in the treatment of a large number of experimental infections of the lower animals, as reported on at the present time; table 28 presents a brief summary of their status in the treatment of various bacterial, virus and

TABLE 28.—*Summary of Therapeutic Value in the Treatment of Human Diseases*

Diseases	Compounds	Results
Local infection of hemolytic streptococcus	Neoprontosil and sulfanilamide	Very good
Hemolytic streptococcic septicemia	Neoprontosil and sulfanilamide	Very good
Streptococcic pneumonia and empyema	Neoprontosil and sulfanilamide	Very good
Streptococcic meningitis	Neoprontosil and sulfanilamide	Good
Erysipelas	Neoprontosil and sulfanilamide	Very good
Scarlet fever	Neoprontosil and sulfanilamide	To prevent complications
Streptococcic peritonitis	Neoprontosil and sulfanilamide	Good
Streptococcus viridans endocarditis	Sulfapyridine	Worthy of use
Ulcerative colitis	Neoprontosil	Good
Meningococcic meningitis	Sulfanilamide	Very good
Meningococcic septicemia	Sulfanilamide	Worthy of use
Pneumococcic pneumonia	Sulfapyridine	Very good
Pneumococcic meningitis	Sulfapyridine	Good
Pneumococcic peritonitis	Sulfapyridine	Good
Gonococcic urethritis	Sulfanilamide and sulfapyridine	Good
Gonococcic ophthalmia	Sulfanilamide and sulfapyridine	Good
Gonococcic arthritis	Sulfanilamide and sulfapyridine	Good
Infections of the urinary tract	Neoprontosil and sulfanilamide	Good
Staphylococcic septicemia	Sulfapyridine and neoprontosil	Encouraging
Undulant fever	Sulfanilamide and neoprontosil	Good
Chancroid	Sulfanilamide	Good
Typhoid fever	Sulfanilamide	Worthy of trial
Clostridium welchii infections	Sulfanilamide, sulfapyridine and neoprontosil	Very good
Tuberculosis	Sulfanilamide	Ineffective
Bacillus pyocyaneus infections	Sulfanilamide	Worthy of use
Pertussis	Sulfanilamide	To prevent complications
Influenzal meningitis	Sulfapyridine and sulfanilamide	Worthy of use
Bacillus friedländer pneumonia	Sulfapyridine	Worthy of use
Rheumatic fever	Sulfanilamide	Doubtful
Tularemia	Sulfanilamide	Worthy of use
Glandular fever	Sulfapyridine	Worthy of use
Lupus erythematosus	Sulfanilamide	Ineffective
Pemphigus	Sulfapyridine	Encouraging
Dermatitis herpetiformis	Sulfapyridine	Worthy of use
Actinomycosis	Sulfanilamide	Worthy of use
Lymphogranuloma venereum	Sulfanilamide	Very good
Measles and pertussis	Sulfanilamide	To prevent complications
Trachoma	Sulfanilamide	Very good
Rabies	Sulfanilamide	Ineffective
Smallpox	Sulfanilamide	Doubtful
Poliomyelitis	Sulfanilamide	Ineffective
Trichinosis	Sulfanilamide	Ineffective

parasitic diseases of human beings. No one can fail to be impressed with the great and remarkable value of sulfanilamide and its derivatives in the treatment of a remarkably wide range of bacterial infections, although they are of limited value in the treatment of virus diseases and those due to animal parasites. Without doubt the discovery of the therapeutic effectiveness of sulfanilamide constitutes the greatest single triumph in therapeutic science, even outranking in importance the discovery of arsphenamine and its allied compounds for the treatment of syphilis and other diseases due to spirochetes.

It is important to mention in this connection, however, that the rational use of sulfanilamide and its derivatives is based more on bacteriologic than on clinical diagnosis, and their indiscriminate use in the absence of the former is to be deprecated. Furthermore, their value in the treatment of local infections, notably streptococcic infections of wounds and burns and suppurative infections, is probably influenced by the presence of pus and debris.

PROPHYLACTIC VALUE

That the possibilities of the prophylactic value of sulfanilamide and its derivatives are worthy of careful attention is readily appreciated. But final appraisal must depend more on the results of carefully conducted animal experiments than on clinical observations, because one cannot be sure in human beings that infection has or would have occurred. Certainly the compounds are rapidly absorbed and eliminated, so that little or nothing is to be reasonably expected from single doses. In other words, prophylaxis demands the presence of effective concentrations in the blood over at least brief periods of time. But this can be readily attained and is probably of definite prophylactic value.

Levaditi and Vaisman were first to study the prophylactic activity of the prontosils in experimental streptococcic infections of mice. Good results were observed when mice were inoculated within forty-eight hours after administration. The period of protection was found to last up to eight days. When the compounds were given parenterally, with slower absorption and elimination, protection endured for as long as twenty-three days. Montestruc observed definite prophylactic effects in rats against experimental streptococcic infections when sulfanilamide was injected in oily suspensions but not when it was given in solution. Hoare has reported that mice can be protected against intraperitoneal infection with hemolytic streptococci by the subcutaneous injection of a single dose of sulfapyridine but that repeated doses are required after infection if the compound is given by stomach. With sulfanilamide, owing to its greater solubility, a single subcutaneous prophylactic injection had but little effect, but good protection was obtained when in addition to the prophylactic dose the compound was given twice daily for three days after infection. As a result of the protection afforded to mice by a single dose before infection followed by several doses thereafter and from investigations on the bactericidal power of the blood of normal human beings, Colebrook and Kenny advocated the use of sulfanilamide as a prophylactic measure in certain circumstances against hemolytic streptococcic infection in the puerperium, but they later considered that their experiments on mice had not been quite conclusive, as equally good results might have been obtained had the

initial prophylactic dose been omitted. Whitby has observed in a large number of tests in vivo and in vitro with sulfapyridine and pneumococci that the compound is not instantly bactericidal or even instantly bacteriostatic. Animals which received the compound prophylactically so that they had a high concentration in the blood at the time of intraperitoneal inoculation with pneumococci nevertheless endured blood stream invasion and multiplication which went on for some hours; yet in twenty-four hours the infection was ended (the "lag" phenomenon).

As previously stated, it is difficult to judge the prophylactic value of neoprontosil, sulfanilamide and sulfapyridine on clinical grounds alone, but the following appear to be reasonable and hopeful applications:

1. In cases of difficult delivery and for puerperal women exposed to streptococcic infection at or near the time of delivery. However, well organized maternity units at present have an incidence of puerperal hemolytic streptococcic infections (group A) not over 1 in 500, and it would be necessary to give prophylactic treatment to thousands of women as well as to observe the equal number of untreated patients before statistical data of any real value could be obtained. But even if the compounds failed to prevent infection they would most likely prevent the rapid development of a localized infection into the more dangerous involvement of the peritoneal cavity or of the large veins draining the urogenital tract with acute or subacute septicemia.

2. For patients exposed to the danger of gas gangrene (Clostridium welchii), especially since the antitoxin is of limited prophylactic value.

3. In epidemics of sore throat due to milk-borne streptococci, although Smith considered sulfanilamide of no prophylactic value against epidemic tonsillitis, presumably because an adequate dose could not be given indefinitely.

4. Possibly for the prevention of extension of hemolytic streptococcic infection to the middle ear and mastoid cells after tonsillectomy in the presence of hemolytic streptococcus; also for the prevention of extension of infection to the lateral sinus or to the meninges from the mastoid cells or nasal accessory sinuses, although, as previously stated, this has been objected to on the basis that it may mask mastoiditis secondary to otitis media.

5. For the prevention of peritonitis following the rupture of a suppurating vermiform appendix and from open wounds of the intestines, since these compounds are highly effective against the hemolytic streptococcus, B. coli and Cl. welchii.

6. For the prevention of hemolytic streptococcic infection after accidental pricking of the fingers in the necropsy or operating rooms.

7. For the prevention of streptococcic infections during the course of rheumatic fever, as suggested by Thomas and France and by Coburn

and Moore, who have obtained promising results with small doses of sulfanilamide given over a considerable period; also for the prevention of the dreaded bronchopneumonia and otitis media due to streptococci of measles and pertussis, as suggested by Thompson and Greenfield.

8. For oral administration to practically all patients with rheumatic heart disease for two days before and two to three days after the extraction of infected teeth or tonsillectomy, as suggested by Long and Bliss. I presume this advice was given principally for whatever value sulfanilamide may have in the prevention of the dreaded and highly mortal subacute endocarditis due to Str. viridans, but since this compound and its derivatives are but slightly effective against nonhemolytic types of streptococci, I doubt if they will show this greatly to be desired prophylactic activity. However, the compound given in this manner may be useful as a prophylactic measure when the foci of infection are largely or entirely due to hemolytic types of streptococci.

9. For prophylaxis of meningococcic meningitis during epidemics of this disease, although a distinct and important objection is the long period of time this would likely require. As previously stated, sulfanilamide does not appear to have prophylactic value against gonorrhea, and according to Felke, the same is true of uleron (sulfanilyldimethylsulfanilamide).

The effective dose for prophylactic purposes cannot be stated at the present time. For the adult Hoare has suggested 15 grains (0.97 Gm.) of sulfanilamide or sulfapyridine every eight hours for at least three or four days, pointing out that protection probably disappears twelve hours after the last dose. These appear to be sensible recommendations for infections with a short period of incubation, but when longer administration is required I suggest for the adult 10 grains (0.65 Gm.) of either compound every eight hours, with smaller doses for children on the basis of body weight.

THERAPEUTIC VALUE OF LOCAL APPLICATIONS

If the successful therapeutic activity of sulfanilamide and its derivatives depends on their uniform permeation of infected tissues by way of the blood, with the possible release or transformation into bactericidal compounds, local applications would appear to be a poor alternative. For this purpose, however, sulfanilamide in 1 per cent solution appears to be the compound of choice, since neoprontosil has much less direct action on bacteria and sulfapyridine is too low in solubility.

In the treatment of meningococcic, streptococcic and pneumococcic meningitis the intrathecal injection of 10 to 30 cc. of a 1 per cent solution of sulfanilamide at the outset of treatment appears to be worth while in order to secure an effective concentration of free sulfanilamide in the cerebrospinal fluid as quickly as possible.

J. L. Brown has injected the soluble prontosil into the pleural cavity in 2 cases of streptococcic empyema, with apparently good results, and Gay and Clark have shown that intrapleural injections of sulfanilamide prevent the development of an otherwise fatal streptococcic empyema in rabbits. Sulfanilamide was used locally as well as orally by Purdie and Fry for the treatment of two sinuses which had discharged pus containing streptococci for three years after parametritis. The rapid healing indicated that chronic as well as acute infections are probably amenable to local applications. Becker and Jaeger have reported good results in the treatment of various cutaneous diseases by local applications of the soluble prontosil and Schranz, in the treatment of infections of the throat by gargling with it, but theoretically a cavity in which the solution can be retained in effective concentration seems a more hopeful site than applications to the skin or mucous membrane. The use of 1 per cent solutions of sulfanilamide, however, would appear to be worthy of trial in the treatment of ocular infections due to hemolytic streptococci, pneumococci or gonococci, because of the ease of frequent applications; it may be also worthy of trial in the treatment of ethmoiditis and sphenoiditis, by instillation with the head in the Proetz position, as well as in the treatment of empyema, peritonitis and wounds.

MODE OF ACTION

In view of the remarkable therapeutic effectiveness of sulfanilamide and its derivatives in infections due to a wide variety of organisms, it is not surprising that considerable effort has been devoted to explaining the precise mechanism by which they produce these results. These efforts have not been alone for the purpose of improving the compounds but because they offer an approach to the mechanism of chemotherapy in general, concerning which there is little precise information.

As stated by McIntosh and Whitby, the theories advanced from time to time may be grouped under the following four heads: (1) that the compounds have a stimulating action on the specific and nonspecific body defenses; (2) that they are capable of neutralizing toxic bacterial products; (3) that they act on bacteria themselves, either as germicides or, in some more subtle fashion, by interfering with invasive power and ability to multiply rapidly, or (4) that they act by some combination of two or more of these mechanisms.

There is, however, little evidence to support the hypothesis that they directly stimulate the specific and nonspecific body defenses. Disposal of organisms exposed to sulfanilamide in vitro and in vivo by phagocytosis has been commonly observed, but it is doubtful if this is due to a direct stimulating effect on leukocytes, as suggested by Tunnicliff. Nor is there any evidence to show that they stimulate the antibody-

producing tissues, with the increased production of such normal or acquired specific antibodies as antitoxins, opsonins, agglutinins and bacteriolysins or such nonspecific substances as leukins and plakins. Nor is there any evidence to support the original hypothesis of Levaditi and Vaisman that they prevent the formation of capsules or destroy those that have been produced.

Furthermore, it is doubtful if they are capable of inactivating exotoxins or endotoxins, although Carpenter and Barbour have recently reported that sulfanilamide protected 87.7 per cent of 80 mice against streptococcus toxin, 84 per cent of 100 against Cl. welchii toxin, 86.7 per cent of 60 against Clostridum botulinum toxin but only 5 per cent of 60 against the toxin of the gonococcus.

But sulfanilamide may prevent the formation of toxins, as suggested by Osgood and Powell. Gay and Clark have observed that under certain conditions it acts on the streptococcus not only by inhibiting growth but by temporarily inhibiting hemotoxin formation, without being able to neutralize hemotoxin already formed. No significant effect, however, was found on the formation of leukocidin or fibrinolysin.

On the other hand, all the available evidence indicates that sulfanilamide and its derivatives inhibit the growth of streptococci and other organisms both in vitro and in vivo, as shown by Keefer and Rantz and by others. The degree of bacteriostasis in vitro is, of course, in relation to the culture medium; if it is poor, bacteriostasis is marked and may even result in complete sterilization, and if it is good, complete destruction of even small numbers of bacteria does not occur. As shown by King, Henschell and Green, sulfanilamide inhibits beta streptococci in tissue cultures, the effects varying directly with the concentration of the compound and inversely with the number of colonies; reduction in hemolysis was observed to accompany bacteriostasis. Stamp has extracted a fraction from a broth culture of group C hemolytic streptococci which is capable of antagonizing the bacteriostatic action of sulfanilamide and sulfapyridine in vitro and apparently free from protein and consists of a mixture of substances of relatively low molecular weight, including free amino acids.

The important question is how sulfanilamide and its derivatives produce bacteriostasis. Available evidence indicates that it is probably the result of neutralization or inactivation of some metabolic or enzymatic activity on the part of the organisms. For this reason the observations of Shinn, Main and Mellon indicating that pneumococci and streptococci may convert sulfanilamide into an anticatalytic compound capable of inactivating blood catalase and thereby allowing the accumulation of hydrogen peroxide, which is destructive for these organisms, command attention, as does the observation by Lockwood that the compound destroys proteases and thereby inhibits bacterial

growth. Also of interest is the theory of Mellon, of Buttle and his associates and of Domagk that the compound interacts with the tissues reciprocally by a process of potentiation resulting in bacteriostasis.

In other words, it appears at the present time that the therapeutic efficacy of sulfanilamide and its derivatives depends on their ability to inhibit the growth of organisms both in vitro and in vivo by interfering with their proliferative activities probably by affecting the metabolic and enzymatic activity. This naturally reduces their invasiveness in vivo, and under the conditions the organisms reduced in numbers are thereby better and more promptly removed by phagocytosis by leukocytes and the cells of the reticuloendothelial system, as well as possibly directly destroyed by natural or acquired bacteriolysins and by such natural nonspecific immune bodies as the leukins and plakins of the blood. In other words, inhibition of growth (bacteriostasis) appears to be the important primary effect, and disposal of the organisms by phagocytosis appears to be the important secondary effect. In this respect sulfanilamide and its derivatives act like "chemical opsonins," in the sense that the organism is first rendered vulnerable or susceptible to phagocytosis by them, as shown by Chandler and Janeway, by Kolmer, Rule and Werner, by Reid and by others.

For a discussion of the relation of chemical constitution to chemotherapeutic action, I can do no better than to quote from Marshall:

> Two lines of research which are being pursued actively at present have for their objectives 1, to obtain more effective and less toxic drugs to use in place of sulfanilamide, and 2, to obtain drugs which are effective in bacterical infections in which sulfanilamide fails. Since many hundreds of compounds have already been tested, we can study to a limited extent the important problem of the relation of chemical constitution to effective chemotherapeutic action. In general only qualitative conclusions can be drawn, because few comparisons of the effectiveness of different compounds have been made in a really quantitative manner; the number of mice used is frequently too small and, due to differences in absorption and excretion, the doses used do not express the correct relation between the compounds. A comparison of compounds on the basis of the blood concentration necessary for a given therapeutic effect would be much more valuable. Another difficulty is the lack of a standard method for assaying the therapeutic value of new compounds. The strain of organism, the virulence and number of organisms used for infection, the amount and spacing of the dosage, the time after infection of administering the first dose, the length of the period of therapy, and the length of time the mice are observed unquestionably affect the quantitative comparison of two active compounds having different ratios of absorption and excretion. The two general methods in use for assaying a new compound are to compare the compound with sulfanilamide on the basis of average survival time of the treated mice or to compare the mortality rates of groups of mice treated with the compound and with sulfanilamide; these two methods probably do not give the same result with all compounds.
>
> So far, all of these newer compounds which have been shown to be active against bacterial infections contain sulfur. It has been demonstrated, however,

that the sulfonamide group is not necessary for activity. Many compounds which do not contain this group and cannot yield it in the body are highly effective as bacterial chemotherapeutic agents. Thus mercaptans, disulfides, sulfinic acids, sulfonic acids, monosulfides, sulfoxides, and sulfones containing an aromatic nucleus have all been reported to have definite therapeutic activity against streptococcus infection in mice. With few exceptions, all of these compounds which are active contain a nitro, amino, or substituted amino group in the para-position to the sulfur.

Considerable information is available concerning the effect of changes in the sulfanilamide molecule on antistreptococcus activity. Little or no activity is found in mononuclear compounds in which either the amino group is replaced by some other group or the sulfonamide group by groups not yielding a sulfonic acid on oxidation. An apparent exception to this is the activity of compounds where the amino group is replaced by a nitro group or azo linkage. This is to be explained by the ready change of such compounds to an amino compound in the organism. A shift of the amino group to the ortho or meta position results in loss of activity; also, a third group in the benzene ring results in loss or lowering of activity. Substitution of amino group by alkyl, aralkyl, substituted alkyl or aryl, acyl, and alkylidene groups in general results in lowering or loss of activity. However, substitution on the amide nitrogen has a variable effect. Methyl and ethyl groups have little effect; higher alkyl groups decrease the activity, and p-amino- or p-nitrophenyl groups are stated to increase it. Compounds of the type of sulfanilyl-sulfanilamide (or polycylic chains of the same general type) have been found active; while with substituents in the parent ring the highest activity is found in the para-derivative, carboxy or sulfonic acid groups in the ortho position in the second ring give the greatest activity. Derivatives of the true disulfanilamide type have been stated recently to be active.

The question of whether or not a real specificity for different organisms exists cannot be answered dogmatically at present. The difference in activity of various compounds against organisms like streptococci, pneumococci and gonococci may be a quantitative rather than a qualitative difference. The fact that diaminodiphenyl-sulfone and 2-sulfanilylaminopyridine are both effective against streptococcus infections, but infinitely more effective against pneumococcus than sulfanilamide, would argue for some sort of specificity, as would the limited data available on the treatment of experimental virus infections.

ABSORPTION, EXCRETION AND DISTRIBUTION

In human beings sulfanilamide is nearly completely absorbed in three to four hours after oral ingestion of moderate doses in capsules or tablets (Marshall); the same is true of neoprontosil, sulfapyridine, sulfanilylsulfanilamide and sulfanilyldimethylsulfanilamide. Sulfanilamide is absorbed much more quickly when taken in solution by mouth than when taken in solid form, apparently because the drug is rapidly absorbed from the intestine (Marshall). Absorption of solutions of sulfanilamide and neoprontosil from the subcutaneous tissues and muscles is even more rapid, and consequently parenteral administration is frequently indicated for the initial dose in severe infections.

After absorption a portion of sulfanilamide is conjugated in the liver (Harris and Klein) into acetylsulfanilamide (the paraacetylamino

derivative of benzenesulfonamide), which is practically inactive against streptococci in mice; with sulfapyridine acetylation is roughly constant for an individual subject and varies widely around 60 per cent in human beings (Long and Feinstone). Both are excreted in the urine partly in the free form and partly as the conjugated compound. Only a small amount is usually unaccounted for in human beings.

The excretion of both free and acetylated compounds occurs mostly in the urine and is rapid (twenty-four and forty-eight hours), similar to that of urea, but reabsorption by the tubules occurs to a greater extent. Elimination is reduced in nephritis with deficient nitrogen excretion, so that greater care is required in dosage in the presence of nephritis. The clearance, however, is definitely increased by an increased rate of flow of urine,[3] which is of some importance in the treatment of gonorrhea and of infections of the urinary tract, in relation to fluid intake. And, as shown by Stewart, Rourke and Allen, precipitation of excreted sulfanilamide in urine at room temperature suggests the possibility of the formation of stones in the urinary tract should the volume of urine become too small during sulfanilamide therapy.

Sulfanilamide resembles urea and ethyl alcohol in its equal distribution in the body; it apparently diffuses readily to all tissues and fluids. This, however, is in relation to vascular supply, so that diffusion in areas of chronic infection, bone and necrotic tissues may be deficient and thus explain deficient therapeutic activity. It is present in saliva (Fickling, Pincus and Boyd-Cooper), pancreatic juice, bile, exudates and transudates in a concentration slightly lower than in blood and readily passes into the cerebrospinal fluid (Marshall). As might be expected, it passes from the maternal to the fetal circulation in pregnant animals and women and is present in the same concentration in the fetal and in the maternal blood.[4] It has produced abortion in rabbits and should be given cautiously during pregnancy. It has been found in human milk[5] in the same concentration as in the blood, or in a higher concentration, but with apparently no toxic effects on nursing infants.

DOSAGE AND ADMINISTRATION

On the basis of rate of absorption and elimination, of the concentration of free sulfanilamide required in the blood for therapeutic effectiveness and of the results of the treatment of experimental infections and human disease, the following principles in dosage and administration of sulfanilamide and its important derivatives appear warranted.

1. Treatment should be begun as soon as possible and preferably after bacteriologic as well as clinical diagnosis has been made.

3. Marshall. Stokinger. Bär.
4. Barker. Lee, Anderson and Chen. Speert.
5. Adair, Hesseltine and Hac. Stewart and Pratt.

2. A large initial dose is indicated, especially in severe or moderately severe infections, in order to produce an effective concentration of free sulfanilamide in the blood as soon as possible. In other words, the principle involved is exactly the same as in serum therapy, namely, to bring about an effective concentration in the blood as quickly as possible.

3. The chosen compound should be given orally when possible. Otherwise an 0.8 to 1 per cent solution of sulfanilamide may be given subcutaneously, intramuscularly or intravenously; or a 5 per cent solution of neoprontosil may be given intramuscularly. A 25 per cent suspension of sulfapyridine in sterile olive oil has been used intramuscularly but may produce marked local reactions. A soluble sodium salt of sulfapyridine (Merck & Co., Inc.) is being used at present by intravenous injection but at the time of writing is not available for general use. The adult dose is ordinarily 1 Gm. dissolved in 25 cc. of saline solution. It should be injected slowly. Accidental perivascular injections produce painful reactions. In England the May and Bell Company have produced a soluble sodium salt (M & B soluble 693) dispensed in a dose of 1 Gm. dissolved in 3 cc. of water for intramuscular (not subcutaneous) injection. It is reported as being not unduly painful and less toxic, with the production of less nausea and vomiting than are caused by the insoluble sulfapyridine by oral administration.

4. Parenteral administration is sometimes preferred for the initial dose and may be required for comatose patients or persons whose vomiting prevents oral administration.

5. The compound should be given every four to six hours day and night for at least several days until improvement occurs, in order to maintain an effective level in the blood and tissues.

6. The concentration of free sulfanilamide and sulfapyridine in the blood varies considerably in different persons, probably in relation to absorption from the gastrointestinal tract. For this reason tests for concentration in the blood are always advisable at frequent intervals for the purpose of adjusting dosage. For this purpose 5 cc. of blood should be removed from a vein about four hours after the preceding dose.

7. For severe infections the dose of sulfanilamide should be such as to maintain a level of free sulfanilamide of 10 to 15 mg. per hundred cubic centimeters of blood (table 29); for sulfapyridine a level of about 5 mg. per hundred cubic centimeters appears sufficient.

8. For moderately severe infections a level of 5 to 10 mg. of free sulfanilamide per hundred cubic centimeters of blood appears sufficient (table 30).

TABLE 29.—*Dosage of Sulfanilamide for the Treatment of Severe Infections*

Weight		First Dose		Every Four Hours*		Total, First Twenty-Four Hours		Daily Maintenance Dose†	
Pounds	Kilograms	Grains	Grams	Grains	Grams	Grains	Grams	Grains	Grams
25	11.3	30	1.9	5	0.3	55	3.5	30	1.9
50	22.7	50	3.2	10	0.65	100	6.5	60	3.9
75	34 to 45.4	60	3.9	15	1.0	135	8.7	90	5.8
125	56.7	70	4.5	15	1.0	145	9.4	90	5.8
150	68.0	80	5.2	20	1.3	200	13.0	120	7.8

1. These doses are usually required for establishing a level of 10 to 15 mg. per hundred cubic centimeters of blood.
2. Calculate dosage according to body weight.
3. Give large initial dose, followed by maintenance dose every four hours.
4. The total daily dose is approximately 1 grain per pound (0.13 Gm. per kilogram) of body weight.
5. Give ½ grain (0.03 Gm.) of sodium bicarbonate with each grain (0.06 Gm.) of sulfanilamide orally.

* Day and night.
† Usually for two to six days; reduce when improvement occurs.

TABLE 30.—*Dosage of Sulfanilamide for the Treatment of Moderately Severe Infections*

Weight		Orally, Every Four Hours*		Total, Twenty-Four Hours†	
Pounds	Kilograms	Grains	Grams	Grains	Grams
25	11.3	5	0.3	30	1.9
50	22.7	10	0.65	60	3.9
75 to 100	34.0 to 45.4	10	0.65	60	3.9
125	56.7	15	1.0	90	5.8
150	68.0	15	1.0	90	5.8

1. These doses are usually required for establishing a level of 5 to 10 mg. per hundred cubic centimeters of blood.
2. Calculate total amount required per day; divide into six parts and give dose every four hours.
3. The total daily dose is approximately ½ grain per pound (0.066 Gm. per kilogram) of body weight.
4. Give ½ grain (0.03 Gm.) of sodium bicarbonate with each grain (0.06 Gm.) of sulfanilamide orally.

* Day and night.
† Usually for two to four days; reduce when improvement occurs.

TABLE 31.—*Dosage of Sulfanilamide for the Treatment of Mild Infections*

Weight		Orally, Every Four to Six Hours*		Total, Twenty-Four Hours	
Pounds	Kilograms	Grains	Grams	Grains	Grams
25	11.3	2½	0.16	15	1.0
50	22.7	5	0.3	15	1.0
75 to 100	34.0 to 45.4	5	0.3	30	1.9
125	56.7	10	0.65	30	1.9
150	68.0	10	0.65	45	2.9

1. Calculate total amount required per day; give dose every four hours for several days and then every six hours.
2. Give ½ grain (0.03 Gm.) of sodium bicarbonate with each grain (0.06 Gm.) of sulfanilamide orally.

* Preferably day and night.

9. For mild infections determinations of the concentration in the blood are not ordinarily required (table 31).

10. For severe infections and in the treatment of patients who cannot swallow or if vomiting interferes with oral administration, parenteral administration of sulfanilamide or neoprontosil is required (table 32).

11. It is frequently advisable to give the drug orally and parenterally, especially in the treatment of severe infections (table 33).

TABLE 32.—*Dosage of Sulfanilamide and Neoprontosil for Parenteral Administration*

	1% Solution of Sulfanilamide			5% Solution of Neoprontosil		
Infection	Per Lb.*	Total in 24 Hrs. per Lb.	Equivalent per 150 Lbs. in 24 Hrs.	Per Lb.*	Total in 24 Hrs. per Lb.	Equivalent per 150 Lbs. in 24 Hrs.
Very severe.....	1 cc.	4 cc.	600 cc. (6 Gm.)	0.2 cc.	0.8 cc.	120 cc. (6 Gm.)
Moderately severe.....	0.6 cc.	2.5 cc.	400 cc. (4 Gm.)	0.1 cc.	0.5 cc.	80 cc. (4 Gm.)

1. This method of administration is to be used in case of vomiting or inability to swallow (comatose state).
2. A 1 per cent solution of sulfanilamide may be used (subcutaneously or intravenously) or a 5 per cent solution of neoprontosil (subcutaneously or intramuscularly).

* Every six hours.

TABLE 33.—*Dosage of Sulfanilamide and Neoprontosil for Combined Oral and Parenteral Administration*

Infection	Total Dose per 20 Lbs. in 24 Hrs.	Oral Dose per 20 Lbs. Every 4 Hrs.	Parenteral Dose per 20 Lbs. Every 12 Hrs.	
			1 per Cent Sulfanilamide	5 per Cent Neoprontosil
Very severe.....	1.2 Gm. (20 gr.)	0.1 Gm.	20 cc. or →	6 cc.
Moderately severe.....	0.8 Gm. (12 gr.)	0.1 Gm.	10 cc. or →	2 cc.

1. This method is always advisable for the first two to six days in severe infections.
2. It may be continued until convalescence is established if full dose cannot be given orally.
3. Give oral doses every four hours and parenteral doses every twelve hours.

12. Intraspinal injections of 0.8 to 1 per cent solutions of sulfanilamide are sometimes advisable at the beginning of the treatment of patients with pneumococcic, streptococcic, influenzal and severe meningococcic meningitis, in order to secure an effective concentration in the cerebrospinal fluid as soon as possible. The amount or volume is the same as that of immune serums.

13. When improvement occurs the total daily dose is reduced or the intervals of administration lengthened, but treatment should be continued if possible until convalescence is well established and cultures are negative, to prevent recrudescence of infection.

14. It is highly probable, however, that organisms may acquire a tolerance for any of the sulfonamide compounds, and whenever resump-

tion of treatment is required it appears preferable to choose another of those available.

15. Apparently sulfanilamide and allied compounds render bacteria more susceptible to immune bodies, and therefore it appears that serum therapy should be used at the same time, especially in the treatment of patients with severe pneumonia or pneumococcic, meningococcic or influenzal meningitis. Blood transfusions and active immunization with vaccines are also helpful in some infections. In other words, it appears advisable not to forego anything of value in surgical drainage, serum and vaccine therapy and transfusion in the treatment of severe infections but to use chemotherapy with these compounds as important adjuvants to treatment.

TABLE 34.—*Dosage of Sulfapyridine for the Treatment of Pneumonia*

Patients	Dosage
Children	Orally: 1 to 1½ gr. per pound (0.13 to 0.2 Gm. per kilogram) of body weight each twenty-four hours; divided into six doses
Adults	Initial dose, orally: 2 Gm. (31 gr.); then 1 Gm. (15 gr.) every four hours for a total of 25 Gm.*
	Intravenously:† 1 Gm. of sodium sulfapyridine dissolved in 25 cc. of saline solution every four to six hours
	Intramuscularly:† 1 Gm. of sodium sulfapyridine dissolved in 3 cc. of water every four to six hours

* Except when treatment is started on or after fifth day (total 15 Gm.).
† For children: less according to age and weight. Especially advisable in the treatment of patients with pneumococcic meningitis.

16. The incompatibilities with other drugs are not well understood at the present time. When sulfanilamide, neoprontosil, sulfapyridine and sulfanilyldimethylsulfanilamide are given orally it is generally advised to avoid the administration of other drugs, but I believe the importance of this has been greatly overrated. Patients should avoid exposure to sunlight or to ultraviolet rays from a lamp while receiving sulfanilamide therapy, because photosensitization appears to predispose to dermatitis.

17. In infections of the urinary tract it is desirable to restrict fluids until the specific gravity of the urine is 1.020 or higher and to give an alkaline diet and alkalis to maintain an alkaline reaction in the urine.

18. Suggested doses of sulfapyridine in the treatment of pneumonia are given in table 34. The dose of sodium sulfapyridine by intravenous injection is about 1 Gm. dissolved in 25 cc. of saline solution every four to six hours by slow injection. Accidental perivascular injections produce severe reactions.

19. The doses of sulfanilamide in the treatment of gonorrheal infections are shown in table 35. The dose of sulfanilyldimethylsulfanilamide for adults is 3 Gm. daily for four consecutive days, or 4 Gm. daily for three consecutive days in divided doses. The total dose for one course of treatment should not exceed 12 Gm. After each course of treatment there should be an interval of seven days during which no sulfonamide medication is given. A maximum of three courses of treatment with sulfanilyldimethylsulfanilamide orally or its sodium salt intravenously should not be exceeded.

20. Watch carefully for evidences of toxicity. The patient should not be allowed to drive a car or to pursue any occupation in which temporary mental confusion or lapse in judgment would be dangerous. The skin should be watched daily for rashes, and the temperature

TABLE 35.—*Dosage of Sulfanilamide for the Treatment of Gonococcic Infections*

Days	Ambulatory Patients Orally, Every Six Hours*	Hospitalized Patients		
		Orally, Every Six Hours*	Neoprontosil, 10 Cc. Dose	Orally, Every Four Hours
First two	1.3 Gm. (20 gr.)	0.65 Gm. (10 gr.)	Every six hours	1.2 Gm. (16 gr.)
Next five	1.0 Gm. (15 gr.)	0.65 Gm. (10 gr.)	Every eight hours	1.0 Gm. (15 gr.)
Next ten	0.65 Gm. (10 gr.)	0.65 Gm. (10 gr.)	Every twelve hours	Reduced dosage
Next fourteen	0.32 Gm. (5 gr.)	0.32 Gm. (5 gr.)	Once daily	

1. There is no unanimity of opinion as to the value of this method.
2. The results are better if the patient is hospitalized.
3. A longer period of treatment is required in females than in males.

* Preferably day and night.

should be recorded for evidences of drug fever. A decision as to whether the compound should be discontinued must depend on the severity of the infection and the degree of reaction. The hemoglobin, erythrocyte and leukocyte estimations should be checked at frequent intervals for hemolytic anemia and neutropenia. Treatment should be stopped if marked reductions occur which are not explainable by other factors.

TOXICITY

Sulfonamide compounds were used in human beings before much was known of their toxicity, pharmacologic or pathologic effects in animals. And while it is too well known to merit comment that chemical compounds may produce toxic effects in human beings which cannot be detected in animal tests, the value of such tests is well known in relation to chemotherapy.

As shown in table 36, the minimal lethal dose of sulfanilamide for mice by oral administration is around 4 Gm. per kilogram. The max-

TABLE 36.—*Toxicity in Animals*

Compound	Author	Maximum Dose Tolerated, per Kilogram Body Weight			Minimum Lethal Dose, per Kilogram Body Weight		
		Mice	Rats	Rabbits	Mice	Rats	Rabbits
Sulfanilamide.....	Raiziss, Severac, Moetsch and Clemence.....	2.0 Gm. (subcutaneously)	0.4 Gm.+ (intravenously)	1.5 Gm. (orally) 0.2 Gm.+ (intravenously)	.....	.....	.....
Sulfanilamide.....	Montestruc.....	.....	.....	.....	4.8 Gm. (orally)	.....	.....
Sulfanilamide.....	Feinstone, Bliss, Ott and Long.....	.....	.....	.....	3.3 Gm. (orally)	.....	.....
Sulfanilamide.....	Marshall.....	.....	.....	.....	3.8 Gm. (orally)	.....	.....
Soluble prontosil.....	Raiziss, Severac, Moetsch and Clemence (1937)	.....	1.0 Gm.+ (intravenously)	.....	.....	.....	0.1 Gm.+ (intravenously)
Sulfapyridine.....	Wien.....	.....	.....	.....	4.2 Gm. (orally)	.....	.....
Uleron*.....	Winthrop Chemical Co., Inc.....	2.0 Gm. (orally)	2.0 Gm. (orally)	5.0 Gm. (orally)	40.0 Gm.+ (orally)	.....	.....
Sodium salt of uleron*	Winthrop Chemical Co., Inc.....	2.25 Gm. (subcutaneously)	2.25 Gm. (intramuscularly)	.....	16.0 Gm. (orally)	13.0 Gm. (orally)	0.25 Gm. (intravenously)
Sodium salt of uleron*	Winthrop Chemical Co., Inc.....	9.0 Gm. (orally)	.....	.....	3.0 Gm. (intramuscularly)	3.0 Gm. (intramuscularly)	.....

* Sulfanilyldimethylsulfanilamide.

imum tolerated dose is about half this amount. The toxicity of sulfapyridine is about the same; sulfanilyldimethylsulfanilamide is apparently less toxic. The rat is thought to be more susceptible than the mouse, and the rabbit is definitely so, as the minimal lethal dose by oral administration is between 2 and 3 Gm. per kilogram of body weight. Dogs appear to be more resistant, while guinea pigs appear to be even more susceptible than rabbits. Little information is available on the toxic effects of repeated doses, but it is apparent that neoprontosil, sulfanilamide, sulfapyridine and sulfanilyldimethylsulfanilamide are remarkably low in toxicity for the lower animals.

TABLE 37.—*Toxic Manifestations*

Manifestations	Frequency	Significance
Dizziness; depression; disorientation	Common	Requires caution in ambulatory patients
Anorexia and nausea	Common	Seldom requires stopping treatment
Vomiting*; acidosis	2 to 5%	Usually prevented by administration of alkalis; may require parenteral administration
Cyanosis	Common	Of little clinical significance
Drug fever	3 to 9%	May be forerunner of hemolytic anemia or agranulocytosis; stop treatment
Dermatitis	1 to 3%	Best to stop treatment temporarily if not urgently required
Mild hemolytic anemia	Common	Not dangerous; watch carefully; treatment may continue
Severe hemolytic anemia	2 to 4% adults 8 to 10% children	Dangerous; stop treatment or continue with transfusions
Transient neutropenia	40 to 50%	Treatment may continue; but watch carefully
Agranulocytosis	Uncommon	Very dangerous; over 80% mortality rate; stop treatment
Toxic hepatitis	Rare	Stop treatment
Hematuria and uroliths*	Infrequent	Stop or reduce treatment; cautious dosage in cases of nephritis
Porphyrinuria	Infrequent	Caution in dosage
Peripheral neuritis†	Uncommon	Stop treatment
Inhibition of spermatogenesis	Doubtful	No significance

* Particularly likely to occur after the use of sulfapyridine.
† Particularly likely to occur after the use of sulfanilyldimethylsulfanilamide.

Hawking has described in cats which died from large doses certain degenerative changes in the spinal cord and brain, and similar changes have been reported in dogs along with acidosis from large doses (Marshall). Similar changes have not been observed in human beings, although the sulfonamides commonly produce cerebral toxic effects of minor degree and likewise polyneuritis in some instances. Contrary to all other observers, Davis, Harris and Schmeisser reported pathologic changes in the liver, kidney, spleen and lung from the administration of the compounds to rats. Hageman reported that sulfanilamide and soluble prontosil had no effect on the liver and kidneys of mice but produced hemosiderosis of the spleen and an increase of eosinophils in the bone marrow. Nelson has also reported histologic changes in various organs of rabbits and hens produced by sulfanilamide and sulfanilylsulfanilamide in doses of 0.5 to 1 Gm. of the former and 1 Gm. of the latter per kilogram of body weight per day.

The toxic manifestations which may occur in human beings are summarized in table 37, along with their frequency, as based on various reports, and their probable significance.

1. *Mental Symptoms.*—It is rather common for ambulatory patients to complain of dizziness, depression, disorientation and decreased mental acuity, especially when large amounts of the drugs are ingested. Judgment may be impaired, and for this reason caution is required on the part of those driving automobiles or engaged in hazardous occupations, and alcohol should be forbidden, as it tends to accentuate these cerebral toxic manifestations.

2. *Anorexia.*—Anorexia is likewise a common complaint but rarely severe enough to stop treatment.

3. *Nausea and Vomiting.*—Nausea and vomiting may occur in a small percentage of patients, especially after the administration of sulfapyridine. This is commonly thought to be due to acidosis with loss of sodium potassium, and for this reason it is generally advised to administer sodium bicarbonate with each oral dose. On the other hand, nausea and vomiting may be due to disturbances of the vomiting center, especially after intravenous injections of sodium sulfapyridine. Some physicians are of the opinion that daily doses of 0.3 Gm. of ascorbic acid in tablets may effectually alleviate or prevent these reactions.

4. *Acidosis.*—An explanation of the acidosis and alkalinity of the urine has been offered by Marshall and Walzl, who have shown that 70 to 80 per cent of sulfanilamide in the glomerular filtrate is reabsorbed in the tubules, which may interfere with the reabsorption of bicarbonate and base. Hartman, Perley and Barnett, however, have demonstrated that although the alkali reserve falls and bicarbonate is excreted in the urine, the p_H of the serum remains constant or even rises, and they have stated the belief that the fall in alkali reserve is an attempt to compensate for a gaseous alkalosis due to hyperpnea. In other words, if this is true, the hyperpnea is primary, possibly through central effect on the Hering-Breuer reflex, with a compensatory fall in alkali reserve.

5. *Cyanosis.*—Some degree of cyanosis is commonly observed, which may become so pronounced as to alarm both patient and family; so it is always wise for the physician to explain the possibility of its occurrence and harmlessness, as it is otherwise of little clinical significance. It is commonly thought to be due to sulfhemoglobinemia, which Archer and Discombe explained was due to catalysis by sulfanilamide of the reaction between hydrogen sulfide and hemoglobin; measures for preventing it are directed to preventing the absorption of hydrogen sulfide from the intestines and include a low residue diet without eggs and the avoidance of all purgatives (especially magnesium sulfate) except liquid petrolatum.

Others have thought that the cyanosis was due to methemoglobinemia (Paton and Eaton), and the intravenous injection of 0.3 to 0.5 Gm. of methylthionine chloride (methylene blue) or the oral administration of 1 Gm. every four hours was originally advised by Hauschild and has since been favorably reported on by Wendel, by Hartman, Perley and Burnett and by Campbell and Morgan, on the basis of converting methemoglobin into hemoglobin. According to Campbell and Morgan, however, it has no effect on the cyanosis due to sulfapyridine. Marshall and Walzl have offered evidence to show that cyanosis may sometimes be due to a cause other than the formation of either methemoglobin or sulfhemoglobin. Ottenberg and Fox have suggested that it is due to the presence of colored derivatives of sulfanilamide produced in the body. Mull and Smith suggested decreased oxygen saturation of the blood as its cause and advocated the administration of oxygen and measures for increasing the capacity of the blood for absorbing oxygen for its relief, but King and Leslie stated that observations on 8 patients tended to indicate that diminished oxygen saturation (increased unsaturation) of the arterial blood did not play any significant role in the cyanosis from sulfanilamide. It is evident, therefore, that its cause is still uncertain; but clinically it can be usually disregarded, and it disappears when administration of the drug is stopped and sometimes even when it is not.

6. *Fever.*—Fever, which may be high, occasionally occurs, and usually the rise in temperature is noted seven to ten days after the beginning of treatment and hence may be mistaken for a recrudescence of the original infection, although in most instances there is no difficulty in reaching a decision, since the fever of infection is likely to have been normal or almost so for a few days before the sharp rise of drug fever sets in. In many respects the condition resembles serum sickness and for this reason has been considered due to allergy, but a more likely explanation is that it is a reaction to the products of lysed bacteria. Hageman and Blake noted its occurrence in 21 of 134 patients, and 9 of these also had a maculopapular erythema of wide distribution, but no evidence could be obtained of sensitization to sulfanilamide. Since drug fever, however, is frequently a warning of impending dermatitis, hemolytic anemia or neutropenia, treatment should be stopped when an unexplained fever develops. The question of safely resuming treatment, however, sometimes arises, and Long, Bliss and Feinstone advised under these conditions administration of 5 grains (0.32 Gm.); if a sharp febrile response is noted within twelve hours it is unwise to continue giving the drug.

7. *Rashes.*—Various rashes may occur, frequently preceded by drug fever and malaise. The eruption is usually maculopapular or morbilliform and brownish red, but sometimes it is purpuric. Usually

almost the entire body is affected, but in some instances the rash is limited to the buttocks or legs or is confined to the palms of the hands or soles of the feet, while the mucous membranes remain unaffected. There is usually no itching or discomfort. With discontinuance of treatment the eruption fades rapidly, and it may disappear anyhow in a few days even when treatment with sulfanilamide is continued. In ambulatory patients it is likely to occur on the exposed parts of the body and may be the result of photosensitization due to porphyrinuria,[6] which the drug is known to cause. The far more serious exfoliative dermatitis has occurred but is fortunately rare. Tedder, who has recently reviewed the literature and reported several cases, divided the patients with dermatitis into those whose condition was precipitated by exposure to sunlight, those definitely sensitive and with low tolerance and those with low tolerance and in whom dermatitis was due to saturation with sulfanilamide but without evidences of allergic sensitization.

8. *Anemia.*—Hemolytic anemia associated with the administration of sulfanilamide was first described by Harvey and Janeway, whose publications were closely followed by case reports by Kohn and Willis. Since then a slowly developing mild anemia with slight reduction in erythrocytes and hemoglobin (10 to 20 per cent) has been commonly observed, especially when treatment is prolonged for ten days or longer. The condition is not accompanied by bilirubinemia, although urobilin is almost constantly present in the urine, and the reticulocytes may be slightly increased, as shown by Campbell, although the increase is not necessarily associated with anemia or leukopenia. Ordinarily it does not require a discontinuance of treatment, but whenever possible the hemoglobin should be estimated and the erythrocytes counted at daily intervals during the first week of heavy sulfanilamide treatment and once or twice a week thereafter, along with frequent examinations of the urine for urobilin as long as medication is continued.

Acute hemolytic anemia, however, has been reported by Wood in 2.4 per cent of a group of 378 adults and in 9.3 per cent of 144 children. It was characterized by rapid reduction in erythrocytes and hemoglobin, moderate to marked leukocytosis, marked reticulocytosis, bilirubinemia with jaundice, urobilinuria and, in certain instances, porphyrinuria, and was one of the most serious of the toxic manifestations of sulfanilamide therapy.

Within twenty-four to seventy-two hours after treatment is instituted the hemolytic anemia usually begins, with nausea, dizziness and fever, and appears to be the result of hypersensitiveness to the compound, without evidence that any one type of infection is a predisposing factor. When the condition is detected treatment should ordinarily stop, although the anemia may continue to progress in some instances and

6. Wien. Rimington and Hemmings.

may recur if and when treatment is resumed. To the best of my knowledge no fatalities have been reported, as the condition readily yields to treatment with blood transfusions and, indeed, if a patient is critically ill, administration of sulfanilamide may be continued along with transfusions to maintain a proper level of erythrocytes and hemoglobin. As reported by Scott and Meerapfel, the prolonged administration of sulfanilamide and uleron (sulfanilyldimethylsulfanilamide) may be followed by an alteration in the type of the blood serum, which precludes the finding of a suitable donor for blood transfusion.

9. *Leukopenia, Neutropenia and Agranulocytosis.*—Mild transient leukopenia and neutropenia with monocytosis may occur in almost 40 to 50 per cent of patients on prolonged treatment with sulfanilamide.[7] This complication usually occurs between the seventh and the twentieth day of treatment and is usually without relation to toxic symptoms but is significant when small doses are employed. It does not ordinarily require cessation of treatment, although when observed it indicates the advisability of daily or almost daily total and differential leukocyte counts for the detection of the more profound changes of agranulocytosis, which is the most dangerous of all the toxic manifestations, since the reported death rate is over 80 per cent. The cause of this profound depression of the bone marrow is unknown but is regarded as due to idiosyncrasy in the same way as with aminopyrine. To the best of my knowledge sulfapyridine is not more dangerous than sulfanilamide and neoprontosil, and agranulocytosis may occur with any of these compounds, especially in debilitated patients under prolonged therapy, since in most reported cases 35 Gm. or more had been taken in a period of two weeks or longer. Unfortunately, according to C. J. Young, examinations of the blood do not always forecast this sudden disaster, but fever or any toxic symptoms require caution in dosage for its prevention.

Among the earliest reports was that of Jennings and Southwell-Sander on 1 case, with the review of 4 others. Since then Johnston has reported 2 cases in which the agranulocytosis due to sulfanilamide and soluble prontosil was fatal and 1 case in which the condition due to sulfapyridine was fatal, and has given a review of 8 cases reported by others in which the conditions were caused by the former compounds. Schwartz, Garvin and Koletsky reported 1 death due to sulfanilamide; Berg and Holtzman, 1 death due to sulfanilamide; Coxon and Forbes and also Nicol and Freedman, 1 death due to sulfapyridine, and Corr and Root, 1 death after sulfanilamide. This does not cover all reported cases by any means, and there were deaths in the majority. Sutherland reported the recovery of a patient in whom the condition

7. Bigler, Clifton and Werner. Britton and Howkins.

was caused by sulfapyridine. Dolgopol and Hobart have observed 2 patients with granulocytopenia (1 of whom died) and 2 patients with leukopenia apparently due to this compound and found that the damage to the bone marrow consisted in depression of the maturation of myeloid cells with occasional disturbance of erythropoiesis.

Apparently prolonged administration is far more dangerous than the giving of large doses over a short period of time, and fever has been the most constant premonitory sign. Of course, the administration of the compound should be promptly stopped and energetic treatment instituted, with repeated blood transfusions, pentnucleotide and liver extract. I have known, however, of 1 patient with agranulocytic angina with a severe hemolytic streptococcic infection to whom sulfanilamide was given in treatment and who made a prompt and satisfactory recovery, in spite of the agranulocytosis and sulfanilamide therapy.

10. *Miscellaneous Toxic Symptoms.*—As previously stated, jaundice may occur in the course of severe hemolytic anemia, but toxic hepatitis is distinctly rare. Cases have been reported by Hageman and Blake and by Saphirstein, 2 cases by Bannick, Brown and Foster, in which the condition was fatal, and 5 cases by Garvin. In a number of these there was also exfoliative dermatitis. A case in which acute yellow atrophy of the liver following sulfanilamide medication was fatal has been reported by Cline.

Renal irritation is also distinctly rare, but Southworth and Cooke have recently reported 3 cases of hematuria associated with abdominal pain and nitrogen retention ascribed to the administration of sulfapyridine. Tsao and his colleagues have reported 5 cases of hematuria due to sulfapyridine in children, 1 of whom died, which they think may be associated with the formation of uroliths, especially since Gross, Cooper and Lewis have produced urinary calculi in 27 of 39 rats by the administration of this compound.

Toxic optic neuritis due to sulfanilamide has been reported by Bucy, 4 cases of peripheral neuritis ascribed to sulfanilylsulfanilamide compounds were reported by Wigton and Johnson, and 1 case of such a condition due to sulfanilamide was described by Ornsteen and Furst. As previously stated, peripheral neuritis has been especially reported in connection with the administration of the sulfanilylsulfanilamide compounds, and while the cause is unknown, most investigators have ascribed its occurrence to the toxic effects of lysed bacteria. Fisher and Gilmour have reported 2 cases in which encephalomyelitis followed the administration of sulfanilamide, with 1 death.

In conclusion, Jaubert and Motz have reported alleged impairment of spermatogenesis following the use of sulfanilamide in the treatment of gonorrhea in 30 per cent of patients; the condition was indicated

by low spermatozoa counts, verging on a state of azoospermia. Harkness, however, as well as Heckel and Hori has not been able to confirm these findings, although Vigoni observed temporary impairment of motility in a proportion of 43 patients, which disappeared after an interval of a month in all but 1. Palazzoli and his colleagues failed to find any effect of sulfanilamide on spermatogenesis in rabbits, although Walker, Sigetti and Wiesner reported that the soluble prontosil may disorganize the germinal epithelium of mice without affecting the interstitial function with the dosage employed.

In relation to the local applications of neoprontosil and sulfanilamide, it is interesting to note that Zaytzeff-Jern and Meleny found that these compounds, as well as sulfapyridine, are not destructive for bacteriophage and may be used with it in the treatment of mixed infections.

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EFFECT OF SULFANILAMIDE ON FIBRINOLYTIC ACTIVITY OF HEMOLYTIC STREPTOCOCCI

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In 1933 Tillett and Garner [1] demonstrated in cultures of hemolytic streptococci a freely excreted extracellular substance which had the property of dissolving solid human fibrin. They also reported that the fibrin from patients recently recovered from hemolytic streptococcic infections often became completely resistant to the fibrinolytic action of hemolytic streptococci. As a result of early observations in this field it was believed that the reaction was a specific immunity response, because patients who had recovered from nonstreptococcic infections did not show this antifibrinolytic reaction. This view is now known to be erroneous, because subsequent investigations by Wadler,[2] Harris [3] and others have demonstrated resistance to fibrinolysis in a small percentage of normal persons and in a large percentage of patients with pneumonia or other infection.

In preliminary studies of normal persons and of patients with various types of infection we were able to demonstrate the fibrinolytic activity of many strains of hemolytic streptococci. Also an antifibrinolytic reaction occurred in several patients who had various types of severe infections. The present study of the effect of sulfanilamide on fibrinolysis was stimulated by the observations in 1 patient in whom hemolytic streptococcic pneumonia developed during a period when he was receiving sulfanilamide. At the beginning of the experiment the man had no evidence of infection, and his blood fibrin was dissolved in normal

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time by a strain of hemolytic streptococcus. Forty-eight hours later pneumonia developed suddenly, with chill, fever, pulmonary consolidation and blood-tinged sputum containing hemolytic streptococci. On the first day of the infection the blood sulfanilamide level was only 3.5 mg. per hundred cubic centimeters, and the fibrinolysis time was not appreciably increased. The dose of sulfanilamide was increased, and within forty-eight hours symptoms of infection had disappeared, the blood sulfanilamide had reached 6.2 mg. per hundred cubic centimeters, and antifibrinolysins had developed. These observations suggested that sulfanilamide might have some effect on the inhibition of fibrinolysis and prompted this study. In vitro experiments by Huntington,[4] however, have shown that fibrinolysis was not affected when sulfanilamide was added in a concentration equal to that found in the body fluids of patients treated adequately by the drug. For this reason and because the fibrin of laboratory animals is naturally resistant to lysis by hemolytic streptococci, our experiments were performed on patients without demonstrable infection.

METHOD

Patients who were normal as far as temperature, leukocyte count and sedimentation rate were concerned were selected as subjects. Preliminary fibrinolysin experiments were made, and patients with a liquefaction time of more than four hours were rejected. Many of the patients in whom mild toxic symptoms developed refused to allow the experiment to be concluded. In 9 experiments in which sulfanilamide was used in therapeutic doses the liquefaction time for each subject's plasma fibrin was determined by a modification of the method of Todd and Garner which was described by Hadfield, Magee and Perry.[5] The same strain of hemolytic streptococci of the same incubation age was used to test both preliminary and subsequent fibrinolysin time on each patient. Because the fibrinolytic activity of some strains is known to diminish with age, control tests of the organism against normal plasma fibrin were carried out. The source of the streptococci, all of beta hemolytic type, is shown in charts 1 to 9. Sulfanilamide determinations in the blood were made according to Marshall's method.[6]

RESULTS

The essential details of the observations are shown in the charts. An increased resistance to fibrinolysis occurred in all patients who

4. Huntington, R. W.: Failure of Sulphanilamide to Prevent Hemolysis, Fibrinolysis and Production of Erythrogenic Toxin by Hemolytic Streptococci in Vitro, Proc. Soc. Exper. Biol. & Med. **38**:328, 1938.

5. Hadfield, G.; Magee, V., and Perry, C. B.: Lysis of Fibrin by Streptococci, Lancet **1**:834, 1934.

6. Marshall, E. K., Jr.: Determination of Sulphanilamide in Blood and Urine, Proc. Soc. Exper. Biol. & Med. **36**:422, 1937.

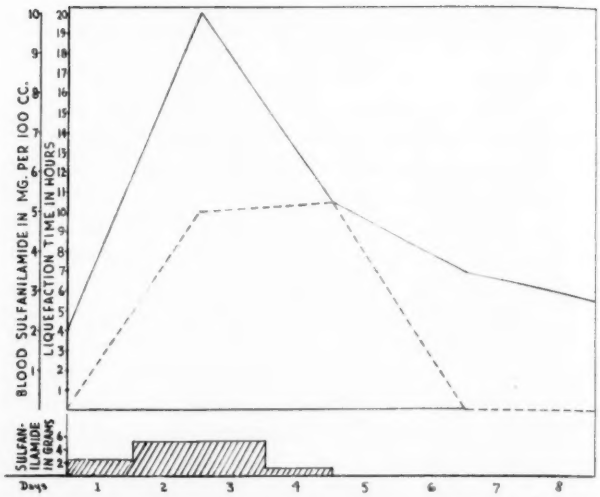

Fig. 1.—G. O., aged 24 (diagnosis: old cerebral concussion), received 10.6 Gm. of sulfanilamide in the first forty-eight hours. The liquefaction time was twenty-four hours, went down to ten and one-half hours in the next two days with the blood sulfanilamide only slightly increased and returned to its normal level after administration of sulfanilamide was stopped. The broken line represents the values of blood sulfanilamide; the unbroken line, liquefaction time.

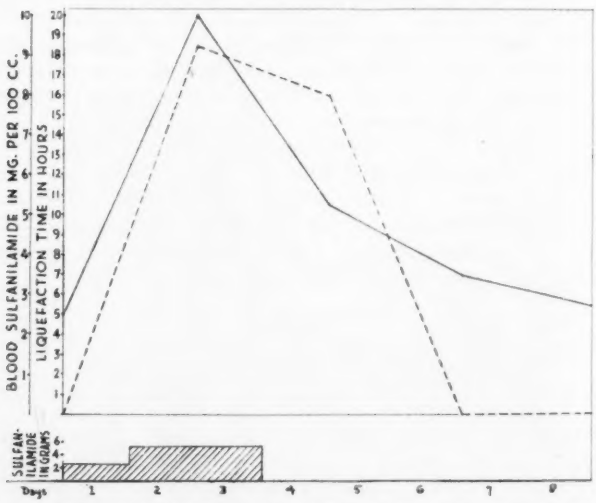

Fig. 2.—T. H., aged 28 (diagnosis: healed duodenal ulcer), had the highest concentration of blood sulfanilamide: 9.2 mg. per hundred cubic centimeters in forty-eight hours. The broken line represents the values of blood sulfanilamide; the unbroken line, liquefaction time.

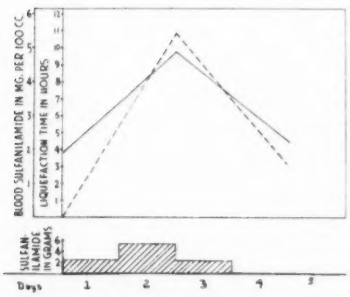

Fig. 3.—F. E., aged 50 (diagnosis: tumor of colon), had a gastric hemorrhage on the third day, and administration of sulfanilamide was stopped. The total amount of sulfanilamide administered was 10.6 Gm. The broken line represents the values of blood sulfanilamide; the unbroken line, liquefaction time.

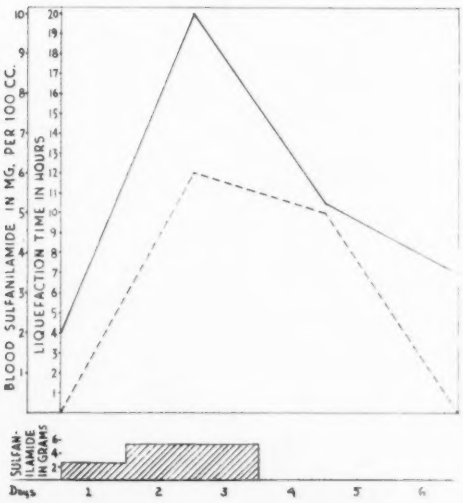

Fig. 4.—R. E., aged 27 (diagnosis: neurasthenia), had a sulfanilamide concentration of 6 mg. per hundred cubic centimeters of blood, with a liquefaction time of twenty hours on the second day. The broken line represents the values of blood sulfanilamide; the unbroken line, liquefaction time.

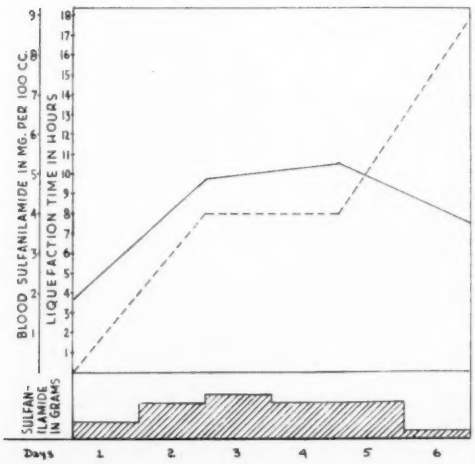

Fig. 5.—H. E., aged 46 (diagnosis: deviation of nasal septum), had a liquefaction time which paralleled the first increase of blood sulfanilamide and dropped slightly on the fifth day, with the blood sulfanilamide concentration rising to 9 mg. per hundred cubic centimeters. The broken line represents values of blood sulfanilamide; the unbroken line, liquefaction time.

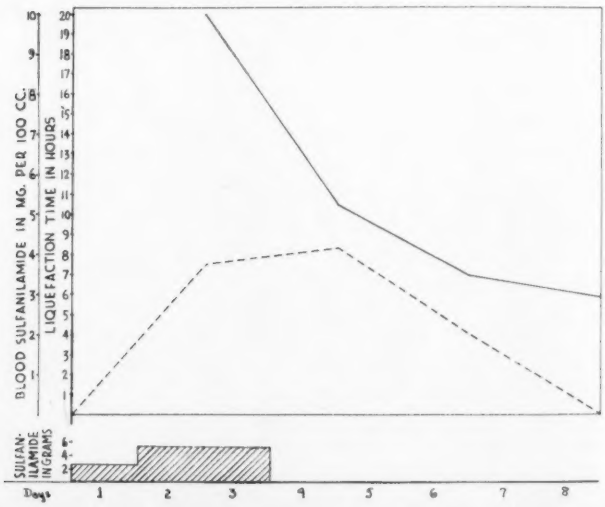

Fig. 6.—J. O., aged 39 (fracture of the right hip), whose control specimen for liquefaction clotted spontaneously, had a liquefaction time of twenty hours after the administration of 13.3 Gm. of sulfanilamide. The broken line represents the values of blood sulfanilamide; the unbroken line, liquefaction time.

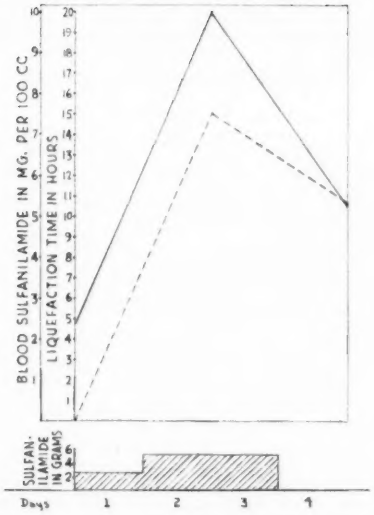

Fig. 7.—S. C., aged 50, was hospitalized for treatment of hammer toe. The liquefaction time (rising to twenty hours) paralleled the blood sulfanilamide concentration. On the fourth day a heart attack developed and the patient died suddenly. The broken line represents the values of blood sulfanilamide; the unbroken line, liquefaction time.

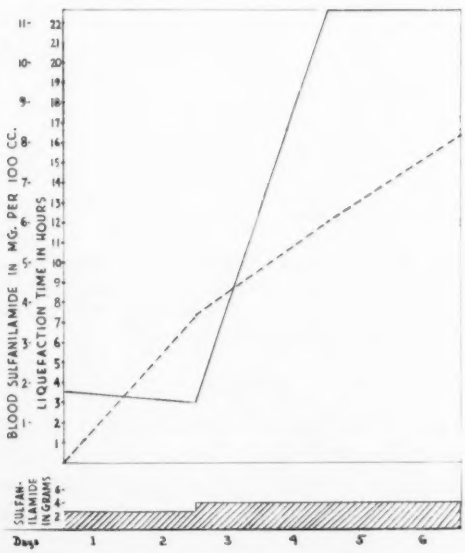

Fig. 8.—W. I., aged 48, had hemiplegia and was taking 4 Gm. of sulfanilamide daily. Streptococcic pneumonia developed on the second day. Liquefaction time was slightly accelerated and subsequently was prolonged to twenty-four hours with recovery. The broken line represents the values of blood sulfanilamide; the unbroken line, liquefaction time.

received therapeutic doses of sulfanilamide. The highest blood sulfanilamide level of the series was 9.2 mg. per hundred cubic centimeters; the lowest, 4.2 mg. Even in patients with blood sulfanilamide at the lower levels inhibition of fibrinolysis occurred. Usually the increase or decrease of liquefaction time parallelled the rise or fall of the concentration of sulfanilamide in the blood. The fibrinolysin time returned to its normal level in from two to five days after administration of the drug had been discontinued.

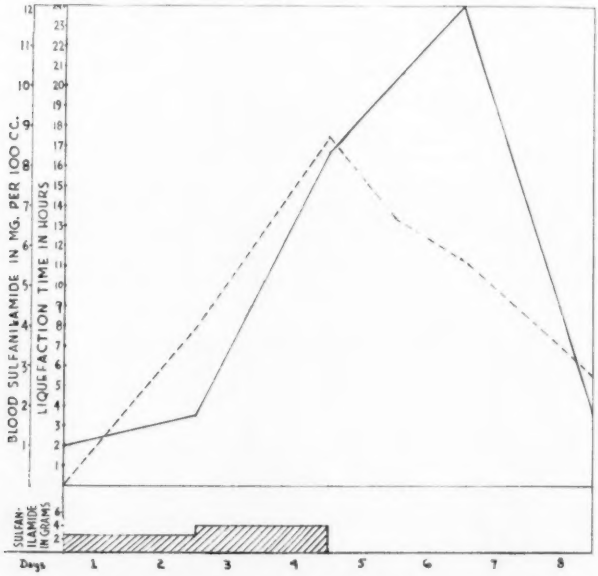

Fig. 9.—C. O., aged 70 (diagnosis: old hemiplegia), had a sulfanilamide concentration which reached 8.7 mg. per hundred cubic centimeters of blood, paralleling the prolonged liquefaction time. The broken line represents the values of blood sulfanilamide; the unbroken line, liquefaction time.

COMMENT

The mechanism of the action of sulfanilamide as an effective therapeutic agent against infections due to hemolytic streptococci and other agents is not completely known. Little or no bactericidal effect can be demonstrated in the test tube. As Gay and Clark [7] stated, this fact

7. Gay, F., and Clark, A.: On the Mode of Action of Sulphanilamide in Experimental Streptococcus Empyema, J. Exper. Med. **66**:535, 1937.

at once points to a necessary adjuvant or determinative action on the part of the fluids or cells of the host. They stated the belief that sulfanilamide produces a bacteriostasis sufficiently marked to protect the accumulated leukocytes and to allow the natural defense macrophages to accumulate. Our observations are compatible with this theory. Gay and Clark suggested further that the resistance of fibrin in the plasma to liquefaction by hemolytic streptococci may play a part in such a bacteriostatic reaction. A further speculation is that sulfanilamide prevents the spread of organisms from an infected focus to regional lymphatics or to the blood stream by rendering the fibrin in tissue spaces around the infected focus insusceptible to the lytic action of hemolytic streptococci.

BLOOD PRESSURES IN AORTIC COARCTATION

STUDY OF PULSE CONTOURS TAKEN BY THE DIRECT METHOD

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Reviews by Abbott [1] and Blackford [2] have shown that about 300 cases of coarctation of the aorta have been reported. In very few of these cases, however, was the diagnosis made during the life of the patient; and studies of the blood pressure were limited by the methods available for estimating it.[3] This communication describes the results of direct optical registration of the blood pressures in various arteries in a case of aortic coarctation when the patient was at rest, during and after temporary occlusion of an artery, coughing and straining, and after administration of epinephrine and of amyl nitrite.

MATERIAL AND METHODS

The subject of these studies, F. H., was a Negro, aged 26, of good physical development but of a very low grade of mentality. On admission to the hospital in 1932, his chief complaint was attacks of pain over the heart and in the left shoulder during the previous two years. He also had shortness of breath, which did not hinder either work or sleep, and complained of headache, slight cough and palpitation after exercise.

The skin, central nervous system, abdomen, skeleton and muscular system showed nothing abnormal on routine physical examination. The electrocardiogram,

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This investigation was aided by a grant from the American Medical Association.

From the Department of Physiology and Pharmacology and the Department of Medicine, University of Georgia School of Medicine.

1. Abbott, M. E.: Coarctation of the Aorta of the Adult Type: II. A Statistical Study and Historical Retrospect of Two Hundred Recorded Cases, with Autopsy, of Stenosis or Obliteration of the Descending Arch in Subjects Above the Age of Two Years, Am. Heart J. **3**:392, 1928.

2. Blackford, L. M.: Coarctation of the Aorta, Arch. Int. Med. **41**:702 (May) 1928.

3. Blumgart, H. L.; Lawrence, J. S., and Ernstene, A. C.: Dynamics of the Circulation in Coarctation (Stenosis of Isthmus) of the Aorta of the Adult Type: Relation to Essential Hypertension, Arch. Int. Med. **47**:806 (May) 1931.

chemical analysis of the blood, blood count and urinalysis revealed no abnormality. The Wassermann and Kahn tests were negative.

Examination of the chest showed normal lungs. There was a slight bulge of the precordium with a diffuse point of maximal impulse. The apex beat was in the fifth interspace, 10 cm. to the left of the midsternal line. No thrills or shocks could be discovered on palpation. The heart was enlarged both to the right and to the left, the right border lying about 4 cm. to the right of the midsternal line in the third interspace, and the other border lying about 13 cm. to the left in the fifth interspace. The mitral valve showed no abnormality except an accentuated first sound. A loud, blowing systolic murmur was heard over the entire sternum both to the right and to the left in the aortic and pulmonary areas and transmitted downward along the right border of the sternum. This murmur was also transmitted into the arteries of the neck and could be heard in the back just to the right of the seventh cervical vertebra. The arteries seemed to be slightly thickened.

The foregoing observations were made in the course of hospital routine, as carried out by interns and passed by the resident, and gave an impression of congenital heart disease, hypertension and moderate arteriosclerosis.

However, when the patient was properly undressed and examined in a good light a number of points were noted which had been overlooked in the routine examination. First, although there were marked activity of the great vessels of the neck, marked precordial heaving and forcible apex impulse, nevertheless there was no evidence of pulsation in the abdominal aorta on inspection, nor could any pulsation be detected in the femoral arteries. These appearances were substantiated by palpation and auscultation, which revealed a very faint femoral pulse and absence of the sounds ordinarily elicited over the femoral arteries. In addition to this, the left external mammary artery was dilated to the size of a chicken quill and was tortuous and visible throughout its length. The same phenomenon was present to a lesser degree on the right side. There were also numerous dilated arteries along the margin of the sternum and in the intercostal spaces, which were easily discernible. From these observations the diagnosis of coarctation of the aorta was made. A roentgenogram revealed erosions along the margin of the ribs such as were described by Abbott [1] and others.

The patient was readmitted in 1936; his condition was practically unchanged except that both the Wassermann and the Kahn reaction were now positive (4 plus).

It was evident that the syndrome was that of coarctation of the aorta; that the aortic "*Windkessel*" was divided into two segments, one above and one below the coarctation; and that the collateral circulation, while adequate to maintain the health of the lower parts of the body, was at the same time sluggish enough to make possible the separate study of the two reservoirs and their branches.

Methods.—Direct simultaneous optical records of the blood pressures were made in branches of the upper and lower arterial systems by means of the hypodermic manometer.[4] This gave an accurate direct measure of the systolic

4. (*a*) Hamilton, W. F.; Brewer, G., and Brotman, I.: Pressure Pulse Contours in the Intact Animal: I. Analytical Description of a New High Frequency Hypodermic Manometer with Illustrative Curves of Simultaneous Arterial and Intracardiac Pressures, Am. J. Physiol. **107**:427, 1934. (*b*) Hamilton, W. F.; Woodbury, R. A., and Harper, H. T., Jr.: Physiologic Relationships Between Intrathoracic, Intraspinal and Arterial Pressures, J. A. M. A. **107**:853 (Sept. 12) 1936.

and diastolic pressures of the same pulsation in both systems and of the transmission time and showed details of the pulse contour.

The arteries of the arm could be entered with a 22 gage needle by simple puncture through the skin, but pulsations of the femoral and dorsalis pedis arteries were so difficult to palpate that surgical exposure of these vessels was necessary. Incision and puncture were done with the area under local anesthesia.

RESULTS AND DISCUSSION

Pressure Values.—The brachial blood pressure as measured directly was 160 mm. of mercury systolic and 100 diastolic. With the auscultatory method the values were 164 systolic and 100 diastolic. In the legs the clinical method gave less accurate results (130 systolic and 100 diastolic against the direct reading of 105 systolic and 80 diastolic).

These observations bear out the findings, discussed in detail in other papers from these laboratories,[5] that variations in the size of the cuff, the size of the limbs, the compressibility of tissue and the pulse contour influence the values obtained by the indirect method. In view of the inaccuracy of auscultatory measurements, all values reported here are those obtained by the direct method. Results are presented in the form of accurate reconstructions of the blood pressure curves. Pressure relationships can be measured to within ± 1 mm. of mercury on any one curve and within ± 2 or 3 mm. on simultaneous curves; and time relations, to within ± five milliseconds.

Comparison of Pulse Contours and Pressures in Different Arteries.—It has been shown elsewhere [4b] that as the pulse wave travels from the aorta out to the periphery the systolic pressure increases. The pulse wave augments and accelerates as it sweeps out, but it levels down to about the same diastolic values in all arteries. As may be seen in figure 1, this increase was noted in the pulse waves in the arm arteries in both the patient with coarctation (*I A*) and the normal control (*IB*); the respective curves do not differ essentially in contour.

In the normal subject this increase in systolic pressure is greater in the aorta and the legs, but in the patient with coarctation the lesion prevented the sweep of the pulse wave through the aorta and the usual augmentation in systolic pressure did not occur (compare curves *II A B* and *C*). The pulse pressure is much smaller below the coarctation than above, because the various collateral channels offer resistance to blood flow and have different pulse transmission times. Consequently, in pulses

5. (*a*) Woodbury, R. A.; Robinow, M., and Hamilton, W. F.: Blood Pressure Studies on Infants, Am. J. Physiol. **122**:472, 1938. (*b*) Robinow, M.; Hamilton, W. F.; Woodbury, R. A., and Volpitto, P. P.: Accuracy of Clinical Determinations of Blood Pressure in Children, with Values Under Normal and Abnormal Conditions, Am. J. Dis. Child. **58**:102 (July) 1939. Hamilton and others.[4b]

taken below the coarctation the upstroke is delayed and slow, the peak is broad, low and rounded and the contour during diastole is almost a smooth curve. There are no landmarks indicating the beginning of diastole. The pulse records taken by the direct method have contours very similar to sphygmographic tracings of the superficial pulses of patients with coarctation of the aorta.[6]

Normally the diastolic pressure and the mean pressure are about the same in the arms and in the legs. In the patient with coarctation (fig. 1, *IIA*) the diastolic value was 6 mm. lower in the legs than in the arms. The mean blood pressure (measured by planimetric determinations of the areas of the respective curves) was 20 mm. less in the legs.

The height of the mean pressure head around the coarctation is of particular interest as an index of the resistance of the collateral circulation. Anxiety and moderate excitement raised it from 20 mm. of mercury (fig. 1, *IIA*) to 29 mm. (fig. 1, *IIB*). This suggests a vasomotor control of the collateral vessels.

Effects of Occlusion.—The pulse wave sweeping out through the artery is changed in contour and height as it meets an obstruction.[7] This is illustrated by the curves recording the pressure in the brachial artery just central to the temporary occlusion produced by digital compression. Figure 1, *III,* shows the original curves of brachial and femoral pressure before and during the occlusion. The systolic pressure increased 50 mm., and the diastolic pressure and the mean pressure went up 3 to 5 mm. in the brachial artery. The femoral pressure rose less than 2 mm. Occlusion of the brachial artery thus produced little effective increase in peripheral resistance. When the femoral artery was occluded in the same manner, there was no change in contour and only a slight rise (10 mm.) in the general level of blood pressure. The rise affected the brachial as well as the femoral pressure and was considered due to an effective increase in peripheral resistance.

Effects of Coughing and Straining.—Coughing elevated the blood pressure in both the femoral and the brachial artery (fig. 1, *IV*).[4b] The source of this elevation of pressure is quite different from the source of the ordinary rise in systolic pressure—the heart. After a cardiac systole, the rise in pressure in the femoral artery is fifty to fifty-five milliseconds later than in the brachial artery. However, the pressure went up in the femoral artery during a cough as soon as, or sooner than, in the brachial artery. This means that the rise in arterial pressure

6. (*a*) Hamilton, W. F., and Abbott, M. E.: Coarctation of Aorta of Adult Type, Am. Heart J. **3**:381, 1928. (*b*) Blumgart and others.[8]

7. Bazett, H. C., and Laplace, L. B.: Studies on the Indirect Measurement of Blood Pressure, Am. J. Physiol. **103**:48, 1933. Woodbury and others.[5a]

EXPLANATION OF FIGURE 1

Fig. 1.—The following abbreviations are used for the arteries: axillary, Ax; brachial, Br; radial, R; femoral, F; dorsalis pedis, D P. T indicates the time interval between appearance of pulse in different arteries; M, the mean blood pressure. Msec. indicates milliseconds; sec., seconds. The term "pulse" refers to a calibrated record of arterial pressure changes during a cardiac cycle.

I A, reconstruction of curves of simultaneous pulses in axillary and radial arteries of patient with coarctation. Blood pressure in mm. Hg, Ax = 163/100, M = 124; R = 172/98, M = 122. T = 50 msec. Time, 0.25 sec.

I B, same as *I A*, normal person: Ax = 110/64, M = 87; R = 118/63, M = 86; T = 49 msec. Time, 0.25 second.

II, reconstruction of curves of simultaneous pulses in the arm and leg. Time, 0.25 sec. *A*, patient with coarctation: Br = 161/88, M = 113; F = 105/82, M = 93. T = 55 msec. *B*, same: Br = 198/110, M = 141; D P = 131/98, M = 112. T = 103 msec. *C*, hypertensive patient: Ax = 183/120, M = 146.5; F = 200/118, M = 146.8; D P = 236/113, M = 143. T from Ax to F = 30 msec.; F to D P = 50 msec.

III, simultaneous pulses from the brachial and femoral arteries of patient with coarctation. Photographs of original records. Occlusion of the brachial artery by digital compression, just below the needle, was started during the diastole of the second beat. Br = 160/91 before occlusion and 208/94 when occluded. F = 101/88 before and 103/89 during occlusion of the brachial artery. Time, 1 second.

IV, effect of coughing on blood pressures in the brachial and femoral arteries of patient with coarctation. *A*, weak cough. *B*, prolonged cough. The upper curves, in continuous lines are, reconstructions of recorded curves. In *A*, the broken lines show the contour of the normal pulse curve. The lower groups of curves represent the excess above normal of the actual arterial pressures; i. e., the contribution of the cough to the pressure.

V, effect of straining on the pulses in the brachial and femoral arteries of patient with coarctation. *A*, strain commences at elevation of curve during diastole; T = 50 msec. *B*, just after commencement of strain; T = 45 msec. *C*, 16 sec. later during straining: T = 80 msec. *D*, just after strain ceases: T = 80 msec. *E*, 5 sec. after *D*: T = 45 msec.

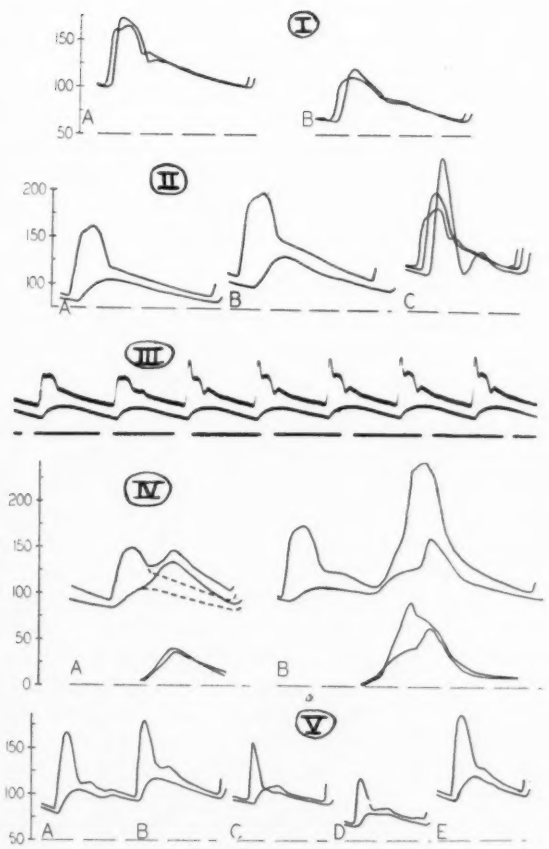
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Figure 1

from coughing appeared both above and below the coarctation, without its propagation through the tortuous channels forming the collateral circulation. The rise from coughing affects simultaneously the aorta and its branches both above and below the coarctation.

When the cough was short and weak, occurring early in diastole (fig. 1, *IV A*), the rise in the femoral pressure (34 mm.) was as large as that in the brachial pressure (32 mm.). These rises in pressure were quite different from those of cardiac origin (fig. 1, *IIA, B*), in which the rise (and hence the pulse pressure) in the femoral artery is far less than that in the brachial artery.

When the cough was stronger, late in diastole and more prolonged (fig. 1, *IV B*) a different picture was seen. At first (as in fig. 1, *IV A*) the femoral pressure increased by the same amount as the brachial, but it failed to continue to do so. The excess pressure produced by the cough became much greater in the branches of the upper reservoir than in the arteries of the leg. However, the femoral pressure rose rapidly with the next systolic filling of the lower arterial reservoir. The elevations of the blood pressure in the femoral and brachial arteries as a result of the cough again became about equal and remained equal as the cough ceased.

The architecture of the diaphragm indicates that the pressure in the abdomen on the lower part of the aorta is just as great as or greater than the pressure in the thorax acting on the upper part of the aorta. Why, then, should coughing cause less rise in blood pressure in the branches of the lower aorta than in those of the upper aorta?

The only explanation that we offer is based on the supposition that the lower reservoir, with its large drainage, becomes depleted before the cough is over, while the upper reservoir, with its smaller drainage, does not become depleted so rapidly. The drainage from the upper reservoir is restricted not only because of the smaller size of the arms as compared with the legs but also because the cough has raised the pressure in the abdomen and the cranial cavity [4b] so as to equal that in the thorax, thus preventing any increase in blood flow to these parts.

When systole occurs, the pressure head around the coarctation is increased, the lower reservoir is replenished and the excess pressure produced by coughing becomes approximately equal in the arteries of the arm and leg.

As show in figure 1, *V*, straining caused the characteristic four phase arterial pressure changes.[4b] At first the pulse contours were not appreciably changed and the increases in systolic and diastolic pressure in the femoral and brachial arteries were the same, 12 mm. systolic and 13 mm. diastolic, indicating that the effects of the strain appeared simultaneously above and below the coarctation. The increases were not propagated

through the tortuous collateral channels but originated from an elevated intrathoracic and intra-abdominal pressure.

In the second phase (fig. 1, *VC*) the pulmonary reservoir became partly depleted. Cardiac filling was inadequate, and the pulsations were somewhat of the empty type, with a lowered pulse pressure. However, they were not mere ripples on the arterial tree, as in the normal person. This is due to the fact that the straining done by this patient was ineffective, elevating the systolic pressure less than 15 mm., as compared with elevations of 35 to 57 mm. reported for the normal person.[4b] Although the patient was well and muscular, he seemed unable to exert himself effectively.

In the third phase (fig. 1, *VD*), when the patient ceased to strain, the pressures fell to the level of the effective intrathoracic and intra-abdominal blood pressures, which had ceased to augment the blood pressure.

In the fourth phase (fig. 1, *VE*), with the reduction of the intrathoracic abdominal pressure the heart became better filled. The systolic and diastolic pressures increased, the pulse pressure widened and the dicrotic notch was higher on the diastolic curve, showing that the arteries were better filled.

Pharmacologic Studies.—Figure 2, *I*, shows the effects of the intravenous injection of epinephrine hydrochloride (0.1 mg.) on pressure contours recorded simultaneously for the radial and the dorsalis pedis artery. Figure 2, *IA*, shows the curve taken just before the injection. The next curve shows the increase in pressure in both arteries eighteen seconds after the injection; evidently the drug had stimulated the heart to greater activity but had not yet caused appreciable constriction of the channels around the coarctation.

Twenty-seven seconds after the injection (fig. 2, *IC*) the radial pressures increased still further, but the pressures below the coarctation actually became lower. The collateral channels had evidently constricted, and the rate of descent of pressure during diastole was increased in both curves. At the same pressures the time required for equal falls in pressure had decreased 15 per cent in the radial artery and 30 per cent in the dorsalis pedis artery. This decrease and the very high peak of systolic pressure in the radial artery probably mean that the distensibility of the great vessels had become less through the action of the drug. It could be interpreted as indicating that the drainage of blood through the arterioles had become greater; but the fact that the cardiac output is diminished shortly after injection of epinephrine [8] and the known action of the drug on arterioles do not render this suggestion

8. Hamilton, W. F.: Some Mechanisms Involved in the Regulation of the Circulation, Am. J. Physiol. **102**:551, 1932.

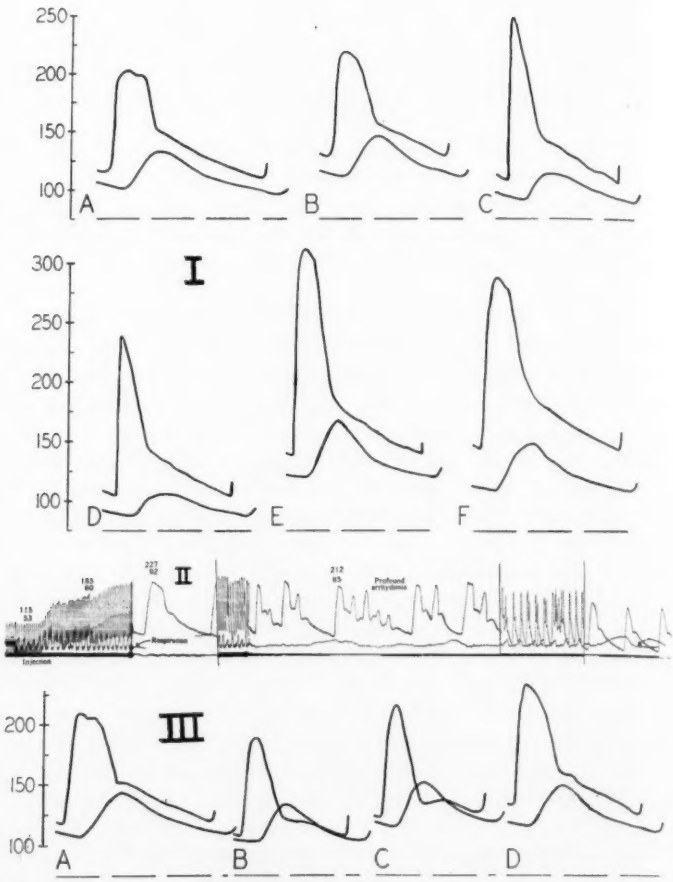

Fig. 2.—The abbreviations in this legend are explained in figure 1. *I*, effects of 0.1 mg. epinephrine hydrochloride injected intravenously on simultaneous pulses in the radial and dorsalis pedis arteries of a patient with coarctation. Time, 0.25 sec. *A*, before injection: R = 203/111, M = 146; D P = 133/98, M = 113; T = 88 msec. *B*, 18 sec. after injection: R = 221/132, M = 165; D P = 147/114, M = 129; T = 75 msec. *C*, 27 sec. after injection: R = 251/110, M = 151; D P = 117/95, M = 106; T = 80 msec. *D*, 33 sec. after injection: R = 238/105, M = 143; D P = 106/88, M = 97; T = 85 msec. *E*, 60 sec. after injection: R = 312/140, M = 192; D P = 167/121, M = 138; T = 82 msec. *F*, 90 sec. after injection: R = 287/144, M = 193; D P = 148/109, M = 125; T = 83 msec.

II, effects of epinephrine in patients with asthma. These original curves show the brachial blood pressure, the respiratory rate and the time in 1 second intervals. At the point marked "injection" 0.2 mg. of epinephrine hydrochloride was injected intravenously. Note the very high blood pressure and the profound arrhythmia. The rate of recording was changed so that some of the cardiac cycles are spread out more than others.

III, effects of 1 pearl of amyl nitrite on the radial and dorsalis pedis pulses in patient with coarctation. *A*, before effect of drugs: R = 209/121, M = 155; D P = 143/110, M = 124; T = 95 msec. *B*, 40 sec. after inhalation started: R = 188/108, M = 133; D P = 133/105, M = 117; T = 85 msec. *C*, 53 sec. after inhalation started: R = 217/128, M = 152; D P = 152/120, M = 133; T = 78 msec. *D*, 90 sec. after inhalation was discontinued: R = 234/126, M = 163; D P = 150/112, M = 129; T = 89 msec.

likely. In the dorsalis pedis artery the increased rate of descent of pressure during diastole is probably contributed to by the lessened diastolic inflow from the collateral circulation.

Sixty and ninety seconds after injection, the main changes seemed to be those due to the building up of the cardiac output, which is known to be a secondary effect of epinephrine.[8] The pressures in both arteries increased, and the gradient of pressure across the coarctation became higher.

These effects of the injection of epinephrine bring out the limitations of the vascular systems of patients with coarctation of the aorta and explain why emotional upsets are especially dangerous to them. In such patients vascular accidents in the upper arterial reservoir and tree and rupture or decompensation of the heart are bound to be far more frequent [1] than in the normal person.

A slightly larger dose (0.2 mg.) of epinephrine hydrochloride was given intravenously to a 22 year old patient with asthma. The brachial blood pressure increased from 115 to 227 systolic and from 53 to 92 diastolic, and profound arrhythmia occurred (fig. 2, *II*). This demonstrates a further toxic effect of epinephrine, that of increasing the irritability of the heart. More emphasis should be placed on the fact that intravenous injections of a 1:1,000 solution of epinephrine hydrochloride are dangerous, even to patients with circulatory collapse.

Inhalation of amyl nitrite produced effects opposite to those of epinephrine (fig. 2, *III*). The effects appeared more slowly because the drug (3 minims, 0.19 cc.) was inhaled over a period of fifty-five seconds. As the drug began to take effect, the radial peak became narrower and lower, the dicrotic pressure less and the diastolic slope flatter; the mean blood pressure decreased 22 mm., and the pulse rate increased. Below the coarctation the rise in systolic pressure was steeper and nearly as great as before the drug was given; the mean pressure was lowered only 7 mm. The resistance of the collateral system had been much reduced by the drug. As is evident, the mean pressure head was lower, and the pressures for both the radial and the dorsalic pedis artery were at similar heights during diastole. The fact that the systolic pressure in the dorsalis pedis artery exceeded that in the radial artery is robbed of much of its apparent meaning by the difference in timing of the two curves.

Fifty-three seconds after inhalation began (fig. 2, *III C*) there was evidence that the collateral system was widely open. The pulse wave was transmitted more quickly across the coarctation. The mean pressure of the upper vessels was not yet back to normal, but that in the lower vessels was well above normal and the mean gradient between the two was still low. Ninety seconds after discontinuing the inhalation of the

drug, the patient was reacting against its vasomotor action by increased cardiac output.[8] The pulse curve for the radial artery gave every indication of a very large stroke volume. The mean pressure below the coarctation was still above normal, notwithstanding the fact that the gradient of the pressure causing flow around the coarctation was again above normal.

It should be pointed out that the reaction to amyl nitrite carries a danger that is particularly marked in this type of patient. The compensatory increase in cardiac output does not in most persons cause the rise in blood pressure seen in this patient whose peripheral outflow was so badly restricted.

The type of pulse which occurs during the period of low pressure is that usually found in the normal person under such conditions. This type of pulse contour would produce the classic superficial pulse forms[9] observed after inhalation of amyl nitrite.

SUMMARY

Direct optical blood pressure tracings were made simultaneously from various arteries of a patient with coarctation of the aorta. Within arteries above the coarctation the systolic pressure was 160 mm. of mercury and the diastolic 88 (mean 113); below the coarctation the pressure was 105 systolic and 82 diastolic (mean 93). Pulse contours recorded from arteries above the coarctation were of normal appearance; from arteries below the coarctation they were flat, smooth and somewhat delayed. This is the opposite of the variation in contour that occurs normally.

Simultaneous rises in pressure produced in the lower and upper arteries by coughing and straining are discussed in detail.

After injection of epinephrine hydrochloride the pressure rose in the upper arteries, and rose and then fell in the lower arteries. Later it rose in both systems. The records indicate that there was an increase in the resistance of the collateral circulation and peripheral arterioles and an increase in the elasticity of the larger vessels.

Inhalation of amyl nitrite produced changes which were generally the reverse of those produced by epinephrine.

Prof. J. H. Sherman and Dr. M. B. Hatcher, of the department of surgery, helped to expose the arteries for puncture. Dr. B. D. Bosworth, formerly of the department of medicine, helped to take the records.

9. Sollmann, T. A.: Manual of Pharmacology, ed. 5, Philadelphia, W. B. Saunders Company, 1936, p. 480.

STUDIES IN DYSTROPHIA MYOTONICA

II. CLINICAL FEATURES AND TREATMENT

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Dystrophia myotonica suffers from an obscurity undeserved because, contrary to general impression, the disease is fairly common, frequently unrecognized and of great general medical interest. Of the 13 patients included in this report, 8 were discovered by the purposeful investigation which we made of the families of our patients previously recognized to have the disease. Of the first group of 5 patients presenting themselves at the Colorado General Hospital for treatment, not one heretofore had had his condition correctly diagnosed. All 13 patients came under our observation between 1935 and 1938. Fleischer's [1] report in 1918, pointing out the hereditary features of the disease, was based on a study of 38 patients seen in the ophthalmic clinic at Tübingen, Germany. Maas [2] in 1937, from the National Hospital for Nervous Diseases in London, published his investigation of 57 families, among which he found 127 unmistakable cases of the disease and 205 suspected cases. Kennedy and Wolf [3a] in 1937 recorded their observations on the effects of treatment with quinine in 18 cases of dystrophia myotonica. In 1938 Kolb, Harvey and Whitehill [3b] added 8 cases to the rapidly mounting number of recently recorded cases. It is evident that the disease is not rare and that the degenerative changes are so widespread that ophthalmologist, neurologist or internist may be called on to diagnose and to treat the disease.

From the Departments of Medicine and Ophthalmology, University of Colorado School of Medicine and Hospitals.

1. Fleischer, B.: Ueber myotonische Dystrophie mit Katarakt: Eine hereditäre, familiäre Degeneration, Arch. f. Ophth. **96**:91, 1918.

2. Maas, O.: Observations on Dystrophia Myotonica, Brain **60**:498, 1937.

3. (*a*) Kennedy, F., and Wolf, A.: Quinine in Myotonia and Prostigmine in Myasthenia: A Clinical Evaluation, J. A. M. A. **110**:198 (Jan. 15) 1938. (*b*) Kolb, L. C.; Harvey, A. M., and Whitehill, M. R.: A Clinical Study of Myotonic Dystrophy and Myotonia Congenita with Special Reference to the Therapeutic Effect of Quinine, Bull. Johns Hopkins Hosp. **62**:188, 1938. (*c*) Wolf, A.: Quinine: An Effective Form of Treatment for Myotonia; Preliminary Report of Four Cases, Arch. Neurol. & Psychiat. **36**:382 (Aug.) 1936.

Patients afflicted with myotonia congenita, or Thomsen's disease, manifest a peculiar difficulty in relaxing muscles which have been contracted. This muscular difficulty is known as myotonia. In Thomsen's disease, most of the skeletal muscles show myotonia and are hypertrophied. For many years patients with myotonia and atrophy of certain muscles, instead of hypertrophy, were thought to have an atypical form of myotonia congenita. In 1909 Batten and Gibb [4] and Steinert [5] independently noted that in these instances the myotonia was limited in distribution and that the muscle atrophy showed a characteristic pattern. The myotonia, they pointed out, was limited mainly to the hand grasp but did at times affect the muscles of mastication and the muscles of the lower extremities. The muscular atrophy involved especially the facial muscles, the sternocleidomastoids, the muscles of the forearm, the extensors of the legs and the dorsiflexors of the feet. In 1912 Curschmann,[6] in emphasizing the importance of the extramuscular dystrophic signs, cataract, baldness, testicular atrophy and various endocrine changes, called attention to the highly characteristic symptom complex of dystrophia myotonica.

Essential details of the case histories of 13 patients with dystrophia myotonica follow.

REPORT OF CASES

CASE 1.—*Myotonia, atrophy, cataracts, baldness, probable testicular atrophy, basal metabolic rate —37 per cent.*

O. M., a 43 year old man, first came to the clinic in December 1935, complaining of poor vision. His oldest sister, N. M., is described in case 2; another sister, J. L., in case 3; a brother, C. M., in case 4, and a nephew, H. M., in case 5 (fig. 1). His father was operated on for cataract at about 60 years of age; a sister of his father was operated on for cataract at 65 years of age; a half-sister of his mother was thought to have had "locomotor ataxia," because of a progressive inability to use her lower extremities from about the age of 30 years to her death at 64 years.

The patient was born in Illinois in 1895. He finished the eighth grade at the age of 16 years. He has been a farmer and worked as a carpenter. He enlisted in the army in 1917 and was discharged in 1919. He had measles, mumps and whooping cough in childhood and pneumonia and pleurisy in 1930. He was married in 1924 and has no children.

The patient has worn glasses since 12 years of age. At the age of 30 he was told that he had incipient cataracts. A few years later his vision began to fail rapidly, and at 40 years of age he was almost blind. Examination at that time revealed almost mature cataracts of both eyes. Slit lamp examination showed an almost complete opacity of each lens, with highly refractile globular opacities, which cast bluish reflections. In January 1936 a cataract was removed

4. Batten, F. E., and Gibb, H. P.: Myotonia Atrophica, Brain **32**:187, 1909.

5. Steinert, H.: Ueber das klinische und anatomische Bild des Muskelschwundes der Myotoniker, Deutsche Ztschr. f. Nervenh. **37**:38, 1909.

6. Curschmann, H.: Ueber familiäre atrophische Myotonie, Deutsche Ztschr. f. Nervenh. **45**:161, 1912.

from the left eye, and in February 1936, from the right eye. At present his vision with glasses is 20/20. For many years he has had some irritation of his eyelids and a slight discharge from his eyes.

In 1922, at the age of 27, he noticed that he had a poor grip, and in 1928 he noticed that if he grasped an object he could not immediately release it. The weakness of his hand grasp has gradually increased; the stiffness has not changed very much. During the last four to five years, on beginning movement after rest the muscles of the lower extremities have felt stiff. The stiffness in his hands and legs is worse in cold weather. He says that when he works his hands seem to be strong, but after resting several days they seem to lose strength.

For the last twelve to fourteen years the patient has been very intolerant to cold, and his hands and feet get cold very easily. During the same time he has lost both strength and energy. In October 1933 he was found to have a basal metabolic

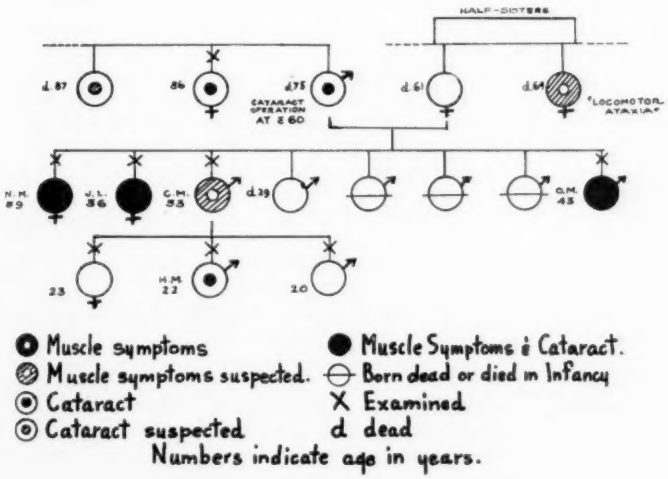

Fig. 1.—Family M. (cases 1, 2, 3, 4 and 5).

rate of —37 per cent. Thyroid was administered, and the basal metabolic rate increased to normal with a dose of 10 grains (0.65 Gm.) one day alternated with 5 grains (0.32 Gm.) the next day. With this treatment the patient's sluggishness and malaise were improved. When seen in December 1935 the patient was still taking thyroid but did not think he was greatly benefited. He felt that there had been no change in the stiffness of his hands. During the last two years in which we have seen him he has not been taking thyroid, and he has noticed little if any difference in his condition.

Physical examination in January 1938 revealed a well nourished, rather tall, fairly well developed white man of 43 years of age, with an expressionless "hatchet facies." He talks rather slowly. The gait is slightly but definitely of the steppage type, with some "slapping." No blepharitis is evident at present. The lens in each eye has been removed. The thyroid is easily palpable and enlarged about one and a half times. The left lobe is somewhat larger than the right

and is firmer than normal, but not markedly so. (The patient believes that his thyroid has been enlarging during the last year.) The lungs and abdomen are normal. The testicles are somewhat smaller and softer than normal.

In the examination of the cardiovascular system, a roentgenogram revealed structures of the heart and aorta to be of normal size and shape. The heart sounds were faint. The blood pressure was 100 systolic and 68 diastolic, and the pulse rate was 56 per minute. The peripheral vessels showed little if any evidence of sclerosis. An electrocardiogram made on Feb. 24, 1938 showed a low voltage of all P waves (the highest being less than 1 mm.), a PR interval of 0.24 second, low voltage of the QRS waves (the largest excursions being 5 mm. in lead II) and normal T waves (the voltage in lead II being 3.5 mm.).

Examination of the neuromuscular system revealed that the patient has the typical myopathic facies, as a result of atrophy and weakness of the muscles of expression. The temporal muscles are moderately atrophied, but the masseters appear in good condition. The sternocleidomastoid muscles are markedly atrophied. The muscles of the forearm are moderately atrophied. The hand grasp is weak, more so on the right, although the patient is right handed. The extensor muscles of the forearm appear more affected than the flexors. Flexion of the thigh and leg is somewhat weakened. Dorsiflexion of the feet is weak, but definite atrophy of the dorsiflexors is questionable. Active myotonia is present to a marked degree in the hand grasp and to a much less degree in the movements of the toes and ankles. The mechanical [7] irritability of the muscles is increased, and mechanical myotonia is evident in the muscles of the chin, the extensors of the wrist and fingers, the tongue, the deltoids and the muscles of the thenar and hypothenar eminences. Electrical myotonia is evident in the muscles of the thenar and hypothenar eminences. The biceps, abdominal, patellar and achilles tendon reflexes are present. The Babinski reflex and the Romberg sign are normal.

The Wassermann test and the Eagle flocculation test gave normal results. Examinations of the urine gave normal results. The blood counts showed no persisting abnormality. A roentgenogram of the skull in January 1936 showed a normal sella turcia and a pineal body, partially calcified, in normal position. The basal metabolic rate on Oct. 15, 1933 was —37 per cent and the value of cholesterol in the blood at the same time was 180 mg. per hundred cubic centimeters. While the patient was taking thyroid, the basal metabolic rates varied from —26 to +8 per cent. In December 1935 three determinations were made of the calcium content of the blood, showing 11.0, 10.1 and 11.2 mg. per hundred cubic centimeters; the associated phosphorus values were 3.8, 3.8 and 3.3 mg. per hundred cubic centimeters.

The results of roentgenologic examination of the gastrointestinal tract on Feb. 18, 1938 were reported as follows: Barium sulfate passed down the esophagus in a normal manner; the stomach appeared of normal size, shape and position; the pylorus seemed to function in a normal manner; definite roentgen evidence of an organic lesion in the duodenum was lacking; the appendix and the gallbladder were not clearly visualized; there was a slight ptosis of the transverse colon; there were spasticity and stasis in the colon, with lack of haustrations in the descending colon and the sigmoid flexures.

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7. When the muscle was stimulated to contract by mechanical or electrical means, we have referred to the "mechanical irritability" or the "electrical irritability" of the muscle and have employed the terms "mechanical myotonia" and "electrical myotonia." When the muscular contraction was voluntary, we have employed the term "active or voluntary myotonia."

CASE 2.—*Myotonia, atrophy, cataracts, basal metabolic rate —31 per cent.*

N. M., a 59 year old white woman, a sister of O. M. (case 1) came to the clinic in July 1937 and gave as her chief complaint a difficulty in walking, which had been present for about one and a half years and appeared to be due to loss of strength in the left lower extremity. When examined in January 1936 she did not complain of this difficulty in walking, although at the time a weakness of the left quadriceps was observed. She is inclined to stumble and fall and has marked difficulty in going up steps. During the last seven years she has at times had difficulty with stiffness in her fingers. When she tries to shovel coal, her hands cramp and she is unable to open them. When her hands are cold or when she is nervous, this stiffness is worse. The hand grasp has become progressively weaker. During the last four to five years she has noticed that at times, when she yawns deeply, her jaw is stiff and she seems temporarily unable to close it. She believes that it may be due to a slight forward displacement of the jaw. Although she never had very much energy and has always tired easily, this condition has become worse in the last six years.

Ever since the age of 22 years, the patient has had red eyelids and sore eyes. At 27 years of age she was fitted with glasses. When she was 46 years of age, ring opacities were found in each lens and small specks of opacity throughout the lens. Her vision with glasses was 20/40 in the right eye and 20/25 in the left eye. Vision has gradually failed but is not as yet very poor.

For the last twenty years or more, the patient has had "stomach trouble," consisting mainly of distention and flatus. The distention begins shortly after eating and lasts a few hours.

She was born in 1879 in Illinois and went through the fourth grade in school. She had whooping cough and mumps in childhood, measles at 22 years of age and smallpox at 28 years. She had pneumonia in 1917 and again several years later. Her menstrual periods began at the age of 12 years and were markedly irregular, usually late, at two, three or four month intervals. The flow was scanty. The menopause occurred at 42 years. She married at 26 years and has never been pregnant.

A physical examination of the patient in September 1937 revealed a fairly tall, well proportioned and well nourished white woman of 59 years, who appeared to react somewhat more slowly than normally. She is not very intelligent but very cooperative. The voice is normal. The abnormal gait appears to be due to some foot drop associated with a difficulty in lifting the left leg. The skin is somewhat dry, and the hair is coarse and dry. Her hands and feet are cyanotic and cold. The left lobe and the isthmus of the thyroid are slightly enlarged, probably because of the presence of a nodule in that region. The lungs and the abdomen are normal.

A chronic blepharitis was observed to be present in each eye. The cornea, the anterior chamber and the iris of each eye are normal. Slit lamp examination showed incipient cataracts, particularly subcapsular and cortical, with typical punctate opacities, some of which had become confluent, under the anterior and posterior capsules. Bluish refractile bodies, occasionally appearing yellow or green, are present in both lenses. The remainder of the media and the fundi show no particular abnormality. The vision is 20/50 in each eye, improved to 20/25 with proper glasses.

In a roentgenogram (September 1937) the heart and the aorta appeared to be of normal size and shape. The blood pressure was 138 systolic and 90 diastolic. The heart sounds were slightly muffled at the apex. Both the first and the second sound

seemed prolonged. The pulmonic second sound was greater than the aortic. The electrocardiogram (September 1937) showed a PR interval of 0.20 second and a left axis deviation; the T waves were normal.

The muscles of expression and the temporal and masseter muscles were somewhat weakened and atrophic. The sternocleidomastoid muscles were markedly atrophic. The triceps and the extensors of the wrist and fingers were weak, but definite atrophy was lacking. The flexors of the thigh were possibly weakened, and the extensors of the thigh and the flexors of the leg were definitely weakened. Dorsiflexion of both feet was weak, and, especially on the left, the dorsiflexor muscles were somewhat atrophied. Mechanical irritability was of normal degree. Mechanical myotonia was observed in the extensors of the hands and fingers, the thenar and hypothenar eminences and the tongue. Electrical myotonia was obtained with strong currents in the thenar and hypothenar eminences. The biceps, triceps and patellar reflexes were present. The achilles tendon reflexes were not obtained. The Chvostek and the Trousseau sign were absent.

The results of the Wassermann and the Eagle flocculation test were negative. The basal metabolic rate in January 1936 was —31 per cent. In January 1936 the calcium and the phosphorus content of the blood were respectively 12.2 and 3.6 mg. per hundred cubic centimeters; the cholesterol content was 148 mg. In September 1937 the calcium and the phosphorus content were 10.0 mg. and 4.6 mg. per hundred cubic centimeters; the cholesterol content was 180 mg., and the plasma chloride content (as sodium chloride) was 658 mg.

Roentgen examination of the gastrointestinal tract in December 1938 showed slight transient cardiospasm; the stomach appeared to be of normal shape, size and position; a slight inconstant defect was noted in the first portion of the duodenum; there was no unusual patency of the pylorus; there was a slight six hour gastroduodenal residue; the appendix and the gallbladder were not visualized; there was a slight ptosis in the transverse colon.

CASE 3.—*Myotonia, atrophy, cataracts.*

J. L., a 56 year old woman, a sister of O. M. (case 1) and N. M. (case 2), was examined in November 1937, in the course of investigations of relatives of our original patients (fig. 1). She complained of attacks of weakness, occurring at intervals of a few weeks to several years for over thirty years. During these attacks she feels faint and weak but she has never lost consciousness and recovers when she lies down for a short time. She has been tiring easily in the last ten years. During the last eight to ten years she has had difficulty in relaxing her hand grasp, especially on exerting a stronger effort, such as pulling weeds. This difficulty is of about the same severity as when it was first noticed. The strength of the hand grasp the patient believes unchanged. During the last few months she has had a soreness in the left thigh, and it has been difficult for her to walk up steps because of an inability to bring the weight up on the left leg. The legs have not been stiff. The hands became cold easily, but there is no special sensitivity to cold.

The patient has worn glasses since the age of 16 years. When she was 52 years old, incipient cataracts were found. She cannot see very well at present. Her eyes are red most of the time and in the morning have "matter" in them.

She had measles and whooping cough in childhood, malaria at 10 years of age, severe mumps at 18 and "walking typhoid" at 20. She was born in Flora, Ill. She did not finish high school. Her menstrual periods started when she was 15 years of age and were never regular. The menopause occurred when she was 43 years of age. She is married and has never been pregnant.

Physical examination in November 1937 revealed a rather tall, well proportioned and well nourished white woman of 56 years. The skin is a pale waxy color which gives her the appearance of being chronically ill. She is alert, fairly intelligent and cooperative. She walks and talks without noticeable difficulty. The thyroid is not enlarged, although the right lobe seems more palpable and more firm than the left. The lungs are normal on percussion and auscultation. The heart is not enlarged on percussion, and the sounds are normal in character. The blood pressure is 122 systolic and 80 diastolic and the pulse about 80. There is no evidence of peripheral sclerosis.

The eyes were examined in May 1938 by Dr. Perry E. Duncan, of Taylorville, Ill., who supplied the following report: "The defect in the lens in each eye is slightly more pronounced than it was on my former examination, in January 1934. The right lens shows a peripheral spoke at 6 o'clock, extending to a point midway between the central and the peripheral portion of the lens. This clouding has the appearance of that usually found in an incipient cataract. The anterior portion of the capsule of the lens shows minute sclerotic areas, which are of sufficient density to account for the impairment of vision. Examination of the left lens shows a peripheral area of clouding, located at 7 o'clock. The density and width of this cataractous area are slightly more pronounced than those of the right lens. The areas of sclerosis on the anterior capsule were more numerous on the lower half of the anterior capsule."

The vision with glasses at that time was 20/32 —1 in the right eye and 20/40 —1 in the left eye. Reexamination of the eyes in November 1938 showed the condition very much as just described, except that the opacity of the left lens had increased until a vision of 20/800 was all that remained. A chronic blepharitis was present.

In an examination of the neuromuscular system in November 1937 a slight ironing out of the facial features appeared to be present and was most noticeable around the mouth. The muscles of the forearm and hand showed no wasting, but the hand grasp on the right was definitely less than on the left and was weaker than normal. Flexion and extension of the right wrist were also weaker than those of the left. Flexion and extension of the left thigh were weaker than on the right and probably weaker than normal. Dorsiflexion of the feet was normal. A definite difficulty and slowness in opening the fist after it had been closed tightly were evident, but the difficulty disappeared after the movement had been repeated four or five times. Mechanical myotonia was present in the tongue, the extensors of the wrist, the thenar and hypothenar eminences and possibly the flexors of the wrist. Electrical examination of the muscles was not made. The biceps and patellar reflexes were present. A Chvostek sign was not present.

CASE 4.—*Myotonia.*

C. M., a 53 year old white man, a brother of O. M. (case 1), N. M. (case 2) and E. L. (case 3), was seen in the course of our investigations (fig. 1). During the last few years this man has noticed that when he works with a hammer or saw his hand clamps around the tool and he often has to use the other hand to get it loose. He says that his "leaders feel tight." The "cramps" vary in intensity and last from several seconds to a half-minute. They are not associated with any pain and occur in both hands but are more noticeable in the right hand, because he uses that hand most. They are worse in the cold. He has no other complaints.

Physical examination in November 1937 revealed that the patient was a well developed and well nourished 53 year old white mna, who appeared to be in good

health. At the time of the examination active myotonia was not elicited. No definite mechanical myotonia could be determined. The general muscle strength was good, and there was no atrophy. Slit lamp examination of the eyes revealed no signs of cataract. The heart was normal in size on percussion. The heart sounds were rather faint but otherwise appeared normal. Extra systoles were frequent. The blood pressure was 130 systolic and 82 diastolic. Electrical examination of the muscles was not made.

CASE 5.—*Cataracts.*

H. M., the 22 year old son of C. M. (case 4), has had trouble with his eyes for over ten years. He has changed glasses repeatedly, and cannot see well at present. He has been told that he has a marked myopia, and two years ago was told that he had "spots in his eyes." There are no other complaints.

Examination in November 1937 revealed an alert, intelligent, ambitious young man. No voluntary myotonia was evident, and the muscles appeared to be of normal bulk and strength. Mechanical irritability was definitely increased, and percussion of the thenar eminences produced muscle contractions persisting only two to three seconds and therefore of questionable significance. The heart was normal in size, and the sounds were normal in character. The blood pressure was 108 systolic and 68 diastolic. The testicles appeared normal.

The examination of the eyes, which was performed in November 1937 by Dr. E. B. Alvis, of St. Louis, showed a myopia of about 4 diopters of each eye and many small bright white dots of variable size in each lens. On the right side these were numerous and had a tendency to collect at the border of the adult nucleus. Others, however, scattered throughout the lens substance, appeared to be more numerous in the periphery than in the center. The left lens had fewer spots, and they were distributed irregularly throughout the lens.

CASE 6.—*Myotonia, atrophy, cataracts, baldness, testicular atrophy, basal metabolic rate —19 per cent.*

J. B., 60 years old, a brother of M. W. B. (case 7) and the father of R. B. (case 8) and M. J. B. (case 9) (fig. 2), stated that he was very well until thirteen years ago, when, during a game of tennis, he noticed a weakness of the right hand. The patient has a peculiar mental attitude. In spite of marked objective evidence of muscular weakness, he denies ever having been conscious of the weakness. His first reaction is to deny everything and then to admit only the possibility of the presence of any defect. It is therefore probable that the weakness has been present for more than thirteen years. The weakness of the right hand has gradually progressed, and atrophy of the muscles of the forearms has become evident. About seven years ago he noticed the atrophy in his left forearm. About two years ago some one asked him how long his legs had been stiff. This, the patient insists, is the first time he realized that anything was wrong with his legs. Since that time his legs have become increasingly stiff and weak. The stiffness is worse after he has been sitting for some time and in cold weather. It is diminished after walking. He stubs his toes when he walks. His articulation has been poor for three to four years.

For several years the patient has had a marked generalized weakness. His hands get cold easily. He has lost about 5 pounds (2.5 Kg.) in the last year, and now weighs about 100 pounds (45 Kg.). His best weight was 134 pounds (60.8 Kg.) at the age of 20 years.

He has been wearing glasses for more than fifteen years. During the last five years, his eyes have been watering, and two years ago he was told that his tear ducts were "stopped up." Vision now is not very good.

He had measles and whooping cough in childhood, a febrile disease ("typhoid-malaria") at 19 years and influenza at 41 and 44 years of age. He was born in Texas, one of twins. The twin brother died at 8 months of age. He went to high school but did not graduate. He has done clerical work and sold insurance. He married in 1909 and has a son (R. B., case 8) and a daughter (M. J. B., case 9). Sexual desire and power were good in his youth and, according to the patient, are still present and unchanged.

On physical examination in September 1937 the patient appeared somewhat older than his stated age of 58 years. He is of medium height and of rather slight build, cooperative and intelligent, but he presents the peculiar mental attitude previously described. He talks in a nasal, monotonous, low-pitched voice, at times difficult to understand. He walks with a definite steppage gait, with the body flexed forward. The skin over the face is tight, thin and shiny. He is bald, and his teeth have been extracted. On examination the thyroid was not enlarged; the lungs and abdomen were normal, and the testicles were definitely smaller and softer than normal.

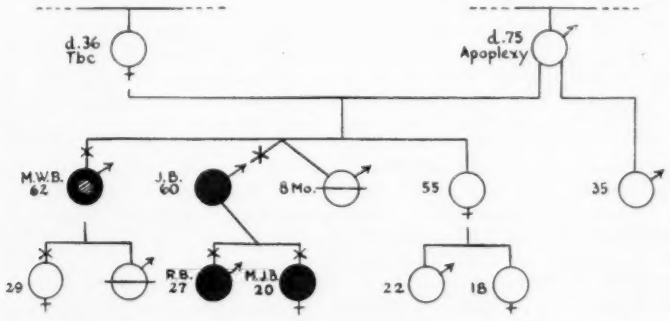

Fig. 2.—Family B. (cases 6, 7, 8 and 9). The legend is the same as for figure 1.

Examination of his eyes showed a chronic conjunctivitis. The cornea, anterior chamber and iris of each eye were normal. The lens in each eye showed early subcapsular and posterior starlike opacities. Numerous small punctate opacities of various sizes occurred throughout the entire lens but were more numerous under the anterior and posterior capsules. With a slightly minus lens, the vision was normal.

The heart and the aorta were of normal size and shape as observed in the roentgenogram. At the apex, the first sound was of moderate intensity and was followed by a rather rough, fairly loud, high-pitched systolic murmur. The first sound was faint at the base. The second sounds were of moderate intensity at the apex and base. There was little evidence of peripheral sclerosis. The blood pressure was 104 systolic and 70 diastolic. The electrocardiogram was normal.

On examination of the neuromuscular system, the temporal muscles were markedly atrophic; the masseters, less so. The periorbital muscles, the muscles of the cheeks and the orbicularis oris were weak and atrophic, the typical myopathic facies being produced. Only a few fibers of the sternocleidomastoids were left. All the muscles of the shoulder girdle and of the trunk showed moderate atrophy. The triceps, the biceps and the muscles of the forearms and hands on each side were markedly atrophied. Flexion and extension of the thigh were fairly good. Flexion and extension of the legs were weak. Dorsiflexion of the feet was very

weak. All the muscles of the lower extremities were somewhat atrophic. Voluntary myotonia was present in the adductors of the thumbs. All the muscles showed a somewhat increased mechanical irritability. Mechanical myotonia was present in the chin muscles, the tongue, the deltoids, the extensors of the fingers and wrists, the thenar and hypothenar muscles, the glutei and the calf muscles. Electrical testing revealed a myotonic reaction, modified by the atrophy. The patellar reflexes were present. The achilles tendon reflex could not be obtained. Chvostek's and Trousseau's signs were lacking.

The results of the Wassermann and the Eagle tests were negative. Examinations of urine and blood gave normal results. The basal metabolic rate in June 1937 was —19 per cent. On June 19, 1937 the calcium and the phosphorus (inorganic) content of the blood were 9.8 and 4.8 mg. per hundred cubic centimeters, respectively; on June 30, 1937 they were 9.1 and 6.3 mg., and on July 1, 1937, they were 9.4 and 4.7 mg. On June 19, 1937 the plasma chloride content of the plasma (as sodium chloride) was 632 mg., and the cholesterol content of the blood was 167 mg.

Roentgenologic examination of the gastrointestinal tract made on Dec. 1, 1937 showed evidence of a marked cardiospasm; the stomach appeared ptotic, but the outline was normal; a small inconstant filling defect was present in the first portion of the duodenum, probably due to a pyloric spasm; a trace of barium sulfate was seen in the stomach after six hours; the gallbladder and the appendix were not seen; there were marked ptosis and stasis in the colon.

CASE 7.—*Myotonia, atrophy, cataracts, baldness, possible testicular atrophy.*

M. W. B., a 62 year old brother of J. B., when examined in November 1937 said that about fourteen years before he had to give up golf because he could not hold the club. At about the same time he observed an atrophy of the muscles of the forearms; since that time both the atrophy and the weakness had gradually increased. Four or five years ago he had noticed difficulty in relaxing his hand grasp, most evident on shaking hands. For ten years or more, owing mainly to trouble with the right foot, he has had some difficulty in walking; in the last three years the left foot has become affected. At the same time he has also noted a stiffness of the legs on starting to walk after he has been sitting awhile. He cannot stand still without losing his balance and has to keep moving around or has to hold on to something.

He is intolerant to cold, and his hands have always been bluish and cold. His distant vision is good, but if he goes without glasses his eyes tire and tear. They have always had "matter" in them in the morning. For several years he has had nocturia and some difficulty in urination. He had measles and whooping cough in childhood and mumps at 28 years of age, followed by orchitis on the left side. Born in Missouri in 1875, he graduated from high school. His work had been clerical and executive. He is married and has a daughter, aged 29 years, alive and well. One child died in infancy.

Physical examination in November 1937 revealed that the patient looks very much like his brother, J. B. He has a similar build but he is much better nourished. He is intelligent and cooperative and is probably telling the truth when he says he "doesn't get excited about anything." He talks with a slight suggestion of nasal twang and walks with a marked steppage gait. He is bald. Examination of his lenses with a hand slit lamp revealed questionable opacities. The lungs and abdomen were normal. The left testicle was markedly atrophic. The right testicle was much larger than the left but appeared smaller than normal.

The heart was not enlarged on percussion. The sounds were rather faint. The pulmonic second sound was louder than the aortic. The blood pressure was 120 systolic and 78 diastolic, and the pulse rate, 92.

When the neuromuscular system was examined it was observed that the patient had the typical myopathic facies. The temporal muscles were somewhat atrophic. The sternocleidomastoid muscles were markedly atrophic. The infrascapular and suprascapular fossae were hollowed. The deltoids were somewhat atrophied; the biceps and triceps on each side were more atrophied, and the flexors and extensors in the forearms were greatly atrophied. The hypothenar eminences were practically gone, and the thenar eminences were atrophied. Flexion and extension of the thigh and legs were good. Dorsiflexion of the feet was very weak, and the dorsiflexor muscles were atrophied bilaterally. Voluntary myotonia was present in the flexors of the fingers and the adductors of the thumbs. Mechanical myotonia was obtained in the tongue, chin muscles and muscles of the thenar and hypothenar eminences and possibly in the calf muscles. The patellar reflexes were not obtained. The Chvostek sign was not present.

CASE 8.—*Myotonia, atrophy, cataracts, testicular atrophy, basal metabolic rate —30 per cent.*

R. B., 27 year old son of J. B. (case 6), was born in Kansas in 1910 and had measles, whooping cough and smallpox in childhood. He has had two years of college work. He has never married. In 1927, at the age of 20 years, on throwing a ball on one occasion, the muscles of the right forearm remained in a painless cramp for several seconds. In 1928 he noticed a weakness in his hands. This weakness progressed rapidly for several years but has been about the same in the last few years. The patient says that until the last two years he had not noticed any wasting of his forearms. He has the same peculiar mental attitude as his father. He denies and minimizes all disability. It appears to be a total indifference to his body but is probably an attempt to conceal any deficiencies. In the last two years he has had a marked stiffness of his hands. This stiffness has probably been present much longer than two years, but in a milder form. It varies from day to day and is worse in cold weather, in the morning and when he contracts the muscles strongly. His legs become stiff when he stays in one position for a time, but he believes that it is no more than normal. In the last year or so he has tended to drag his feet, especially the left, and he is more likely to stumble. In the two years since he has had his teeth extracted he has had some difficulty in pronouncing certain words.

The patient dislikes cold weather. His hands and feet get cold easily and feel numb when they are cold. During the last few years he has been fatigued easily. Sweat secretion has been normal. His mouth is rather dry. His hair has been getting thinner.

He has worn glasses since 1930 when his vision became poor and he began having headaches. At present he can see well with glasses. Three years ago he got some poison weed in his eyes and since that time his eyes water and have "matter" in them in the morning.

On physical examination in January 1938 the patient was observed to be of medium height and rather slight build. He is cooperative and intelligent. His voice is definitely but not markedly nasal, and his gait is slightly "slapping." There is some ironing out of expression with a smooth, unwrinkled appearance of the skin. The hair appears to be of normal distribution and abundance. The teeth are out. The thyroid is not enlarged but is possibly more firm than normal. The lungs and abdomen are normal. Both testicles are small, soft and definitely atrophic.

Examination of the eyes revealed a marked type of chronic conjunctivitis. Until the pupil was dilated, no opacity was noted in the lens. A slit lamp examination showed some small refractile punctate dots in the subcapsular area

near the equator of the lens in both eyes and several needle-like projections of opacity extending for a few millimeters from the equator toward the center. The vision in each eye was 20/20 with a lens correcting a moderate amount of compound myopic astigmatism.

The heart and the aorta as shown in a roentgenogram (January 1938) are of normal size and shape. The heart sounds were observed to be of normal character, and no murmurs were present. There was no evidence of peripheral sclerosis. The pulse was of good quality and of regular rhythm. The blood pressure was 100 systolic and 80 diastolic. The electrocardiogram (January 1938) showed a PR interval of 0.20 second and a slight left axis deviation.

When the neuromuscular system was examined, the muscles of expression were found to be weak, with a suggestion of myopathic facies. Atrophy of the temporal muscles was fairly marked. The sternocleidomastoid muscles were markedly atrophied. All the muscles of the shoulder girdle and upper extremities were atrophied, but the atrophy was farther advanced in the muscles of the forearm and in the thenar and hypothenar eminences than in the upper part of the arm and the shoulder. Flexion and extension of the thigh and knee were good. Dorsiflexion of the feet was weak. Voluntary myotonia was present to a marked degree in the hand grasps. Mechanical myotonia was marked in the tongue, the chin muscles, the triceps, the biceps, the flexors and extensor muscles in the forearm, the thenar and hypothenar eminences, the thigh muscles, the calf muscles and the dorsiflexors of the legs. It was present in a less degree in most of the other muscles. Electrical myotonia was obtained in all the muscles of the upper extremities, the only region examined. The triceps, patellar and achilles tendon reflexes were present. Chvostek's sign was probably negative; a twitch was obtained which appeared to be due to muscle irritation rather than to nerve stimulation. Trousseau's sign was lacking.

Reactions to the Wassermann and the Eagle test were negative. Examinations of the urine and blood gave negative results. The basal metabolic rate in January 1938 was — 30 per cent. On Jan. 5, 1938 the calcium content of the blood serum was 10.1 mg. per hundred cubic centimeters; the phosphorus (inorganic) content of the serum was 4.6 mg.; the cholesterol content of the blood was 143 mg., and the chloride content of the plasma (as sodium chloride) was 618 mg. A roentgenogram of the sella turcica taken on Jan. 5, 1938 showed it to be very small but of smooth outline.

Roentgenologic examination of the gastrointestinal tract on January 5, 1938 revealed a slight cardiospasm; the stomach was slightly ptotic; there was a small six hour gastric residue; the pylorus functioned normally; the gallbladder and the appendix were not definitely visualized; marked ptosis of the transverse colon was present; the colon was insufficiently filled with barium sulfate for definite diagnosis.

CASE 9.—*Myotonia, atrophy, cataracts.*

M. J. B., 20 year old daughter of J. B. (case 5) was examined in March 1938 in the course of the investigation of the family. She had noticed a slight stiffness in her hands in the cold since the age of 13 or 14 years. When she grasps an object such as a door knob in the cold she cannot let go readily. She does not believe that the severity of the condition has increased in recent years. She has no stiffness of the feet or jaws and no difficulty in walking. She says that she has noticed no weakness but that her fiancé says that she "seems to play out easily, sleep a lot, and doesn't seem as strong as she should." Her hands and feet are usually cold.

She has always had a high-pitched voice. She wore glasses from the ages of 7 to 12 years and started wearing them again during the last year.

Her menstrual periods started at 15 years of age, have been regular, at thirty-one day intervals, and usually occur with little or no pain. Each period lasts four days, and the flow is about normal.

She had measles and smallpox in childhood. Her tonsils and adenoids were removed six years ago.

Physical examination in March 1938 showed the patient to be a somewhat undernourished, slightly built woman of 20 years. She is very active and cooperative and responds rapidly, but she attempts to minimize and conceal any defects. Her voice is irritatingly high pitched. Her gait is normal. Her jaws are narrow, with a high-arched palate and a crowding of the teeth. The thyroid is normal in size but possibly firmer than normal.

Examination of the eyes after dilation with homatropine revealed some very fine, almost dustlike highly refractile bodies throughout the periphery of the cortex of both lenses. Under the slit lamp the opacities ranged from blue and green to red. She had no other demonstrable ocular pathologic condition. Her vision in each eye was 20/20 with a correction for myopic astigmatism.

The heart and the aorta were observed to be of normal size and shape, as shown by a roentgenogram (March 1938). The blood pressure was 106 systolic and 70 diastolic. The heart sounds were normal. A systolic murmur of moderate intensity was present. It was loudest in the pulmonic area, faded somewhat in the third and fourth interspaces and increased again in intensity at the apex. The electrocardiogram (March 1938) showed a tendency to right axis deviation and a PR interval of 0.20 second. The temporal muscles were definitely weak and somewhat atrophied. The periorbital muscles were weak. The sternocleidomastoids were weak and atrophic. The triceps on each side was definitely weak; the biceps and the muscles of the forearm were questionably weak. Strength in the lower extremities was good, except possibly for weakness in the flexion of the legs. Mechanical irritability appeared increased. Mechanical myotonia was present in the tongue, chin, thenar and hypothenar eminences, flexors and extensors of the forearms and calf muscles. The biceps, triceps, abdominal, patellar, and achilles tendon reflexes were present. Trousseau's sign was absent, and Chvostek's sign was equivocal, probably negative.

CASE 10.—*Myotonia, atrophy, cataracts, basal metabolic rate —10 per cent.*

J. M., a 46 year old white woman, first came to the clinic in March 1936, complaining of difficulty in walking. A 31 year old sister had a cataract removed a few months previously, and another cataract was soon to be removed; a 34 year old sister (S. E., case 11) had early cataracts typical of dystrophia myotonica; her father had one cataract removed at the age of 61 years and another at the age of 64 years; a sister of her father had a cataract operation at about the age of 50 years (fig. 3).

Except for poor vision the patient was apparently well until she had typhoid fever in 1915. A year later she noticed a difficulty in opening her fist after clenching the hands tightly, a symptom which has persisted in marked degree to the present time. During the past eleven years, the hands have very slowly become weak. In the last eight years, on awaking in the morning, the patient has had difficulty in opening her eyes. The eyelids seem "heavy and stiff" and it is twenty to thirty minutes before she can keep her eyes completely open; occasionally she has to use her fingers to open her eyes. During the past nine years, if she yawns widely her lower jaw slips out of place but can be readily replaced by pressure. Three years ago weakness began in the left leg, which

she first noticed as a tendency of the leg to "stay behind." The left ankle "turns" easily, and she has great difficulty in walking up stairs.

For many years she has felt weak and without energy, but in recent years this has been worse. Her hands and feet are cold all the time. A loss of hair, which has been noticed in recent years, has become more marked in the last two years. Her vision was poor while going to school, and she began to wear glasses at the age of 24 years. The vision gradually decreased, and at 34 years of age she was told that she had cataracts. She had the cataract removed from the right eye in 1930 and from the left eye in 1933.

She had whooping cough and measles in childhood, an appendectomy and removal of gallstones in 1919, and an operation to drain an infected toe on the left foot in 1916.

Her menstrual periods started at the age of 16 years, and she said they had been regular and normal until two years ago. Since that time they have become markedly irregular, and the discharge was usually excessive in amount. She married at the age of 35 years and has had no pregnancies.

Physical examination of the patient in March 1936 showed her to be a well nourished white woman of medium stature. She is mentally alert and cooperative.

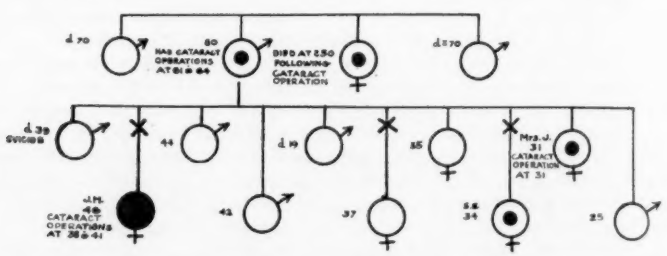

Fig. 3.—Family D. (cases 10 and 11). The legend is the same as for figure 1.

She walks with a slight limp, probably due to a "dragging" of the left leg. Her voice has a nasal quality. The skin of the hands is dry, shiny, cracked, rather inelastic and bluish. The same is true to a less extent of the skin of her feet. The thyroid is not enlarged. The lungs and the abdomen showed nothing abnormal.

Examination of the eyes showed a chronic blepharitis. Both lenses had been removed.

Except for a slight splitting of the pulmonic second sound, the heart sounds were normal in character. Peripheral sclerosis was not evident. The blood pressure was 116 systolic and 80 diastolic. A roentgenogram taken in April 1938 revealed the heart and aorta to be of normal size and shape. An electrocardiogram taken on Jan. 15, 1937 showed the following characteristics: very low voltage of the P waves in all leads; QRS waves of lowest voltage in lead I and notched in lead III; questionable Q waves in lead I; no Q waves but definite S waves in leads II and III; upright T waves of rather low voltage in leads I and II; inverted T waves in lead III. On April 24, 1937 the following changes in the electrocardiogram were noted: The voltage of the QRS waves in lead I was somewhat increased and exceeded that of lead III; no Q waves were present, but a definite S wave occurred in leads I, II and III; the ST segment was isoelectric in all leads; T_1 was now inverted; T_2 was still upright but of lower amplitude; T_3 was upright;

a Q wave was present in lead IV (Wolferth) and the T wave was upright. On April 11, 1938 the following changes were noted: QRS voltage was again lowest in lead I, but the presence of a Q_1 wave was questionable; the spread of the QRS waves was 0.11 seconds; T_1 was practically isoelectric; T_2 was somewhat greater in amplitude than on April 24, 1937, but less than on Jan. 15, 1937; T_3 was practically isoelectric; T_4 was diphasic. In the period between the first two electrocardiograms, this patient had complained of shortness of breath. This was probably not as evident as it might have been if the patient had not been markedly limited in her activity by the muscular disorder. This shortness of breath gradually left, over a period of several months. It appeared likely that sometime between the first two electrocardiograms this patient had a myocardial infarction involving the anterior surface of the left ventricle. During this period the patient had received intravenous injections of a quinine salt on a few occasions, and the question arose as to the possible relationship of this medication to the electrocardiographic evidences of myocardial damage.

Examination of the neuromuscular system in March 1936 showed that the periorbital muscles, the temporal muscles and the muscles of the cheeks and mouth are weak and atrophic, typical myopathic facies being produced. The masseter muscles are weak and atrophic. The sternocleidomastoids are markedly atrophic. The trapezii, the deltoids and the muscles of the suprascapular and infrascapular fossae showed moderate weakness and some atrophy. The flexors and the extensors of the fingers are weak; atrophy is moderate. The thenar and hypothenar eminences are somewhat atrophic. Flexion of the left thigh and leg is definitely weak, and extension of the left leg is weak. This is also true to a less extent on the right leg. On both sides, dorsiflexion of the foot is weakened. Voluntary myotonia is marked in the hand grasps. Mechanical myotonia is present in the tongue, the chin muscles, the sternocleidomastoids, the deltoids, the extensors of the wrists and fingers, the muscles of the thenar and hypothenar eminences, the calf muscles and the peroneal muscles. Electrical myotonia was demonstrated in the muscles of the thenar and hypothenar eminences. The biceps, triceps, patellar and achilles tendon reflexes were not obtained.

The results of the Wassermann test and the Eagle flocculation test were negative. Several examinations of the urine and blood counts gave normal results. On March 11, 1936 the calcium content of the blood was 10 mg. per hundred cubic centimeters; the phosphorus content was 3.3 mg.; the cholesterol content was 230 mg., and the sugar content was 78 mg. Examination of the spinal fluid on Dec. 18, 1935 showed it to be normal. The basal metabolic rate on March 10, 1936 was —10 per cent.

Fluoroscopic examination of the gastrointestinal tract in March 1938 revealed normal peristaltic waves along the course of the esophagus; the radiopaque material descended normally down the esophagus into the cardiac portion of the stomach; the stomach appeared to be of normal shape, size and position; the pylorus seemed to function normally; there was no roentgen evidence of organic disease in the stomach or duodenum and no six hour gastroduodenal residue; the gallbladder and the appendix were not definitely visualized; ptosis of the transverse colon was present.

CASE 11.—*Cataracts.*

S. E., aged 35 years, sister of J. M. (case 10), was examined in 1936 in the course of the investigation of the family (fig. 3). She had no complaints, and the only positive physical finding was the presence of typical early cataracts. Many small subcapsular spherical opacities, a few confluent, were found throughout the

cortex of the lens of each eye, especially toward the equator. In the beam of the slit lamp they appeared to be green and blue. The vision was 20/20 in each eye.

CASE 12.—*Myotonia, atrophy, cataracts, basal metabolic rate —20 per cent.*

N. P., a 54 year old white man, said that his father was operated on for cataract at the age of 55 years; a brother who died at 33 years of a "heart attack" had a cataract operation at 30 years of age and typical muscular symptoms; a sister who died at 42 years of age had cataract operations at the age of 37 years and typical muscular symptoms; a sister aged 48 years had poor vision and marked atrophy (fig. 4).

At about the age of 36 years, the patient noticed that when he started to eat, on taking the first bite his jaw would stay clamped for a few seconds before he could release it. After the first bite this would disappear. This lasted for about two years. At about the same time he noticed difficulty in releasing objects when he grasped them in his hand. Soon after, he began to have a weakness of his

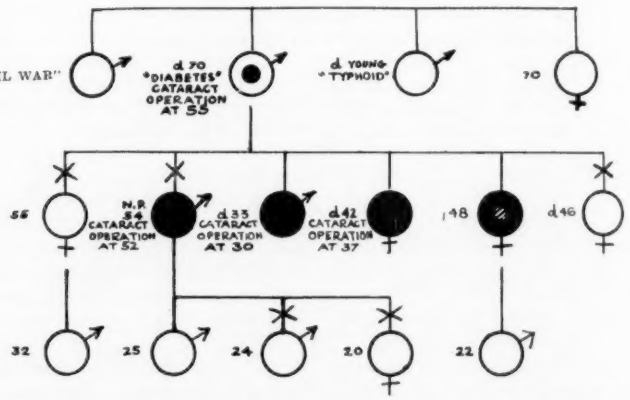

Fig. 4.—Family P. (case 12). The legend is the same as for figure 1.

hands, and he had to quit his job as a train conductor. The muscles of the hands had atrophied and become markedly weakened, especially in the last nine years. The stiffness left the fingers as they became weaker and is now present only in the thumbs. The arm muscles have also become weak and have atrophied somewhat. A "slapping" gait, which was noticed about five years ago, has shown little if any progression in the last two years. During the last few months the patient has noticed a stiffness of his legs in the morning; this leaves after he takes a few steps. For the last three years his voice has had a nasal quality, and he has noticed that in drinking from a fountain a little water at times comes back through his nose. In swallowing, at times, food seems to "stick in his throat."

In about 1925 he was told that he had a cataract. His vision gradually failed, and in 1936 he had the cataract removed from the right eye. The left eye also has a cataract. His hair started falling out at about the age of 18 years, and he was bald in his thirties.

He had typhoid fever and scarlet fever at 9 years of age, pains in the joints and fever at 32 years and influenza at 34 years. He was born in Indiana in 1884 and graduated from high school at 16 years of age. He has worked as a clerk, brake-

man, conductor and insurance salesman. He married in 1910 and has three children. He says that his libido and potency have always been normal.

Physical examination in September 1937 revealed the patient to be a well nourished white man who appeared to have had a good muscular development at one time. He is fairly intelligent and very cooperative. He talks in a rather monotonous voice which has a definite nasal quality. He lifts his legs high as he walks and has a definite "slap" in his gait. He is bald. Examination showed the thyroid to be firm and nodular, with some enlargement of the right lobe. The lungs were normal. Abdominal examination gave negative results. The testicles were of normal size.

Examination of the eyes early in 1936, before the cataract operation, revealed a very stubborn ulcerative blepharitis of the lids and a chronic conjunctivitis. The eyes were normal except for the cataracts, which appeared as small, round, highly refractile, most frequently subcapsular opacities, throughout the cortex of each lens. A marked posterior polar cataract of the stellate variety, which gave a golden appearance with the slit lamp, was present in both eyes but was more marked in the right eye. The vision was 20/200 in the right eye and 20/40 in the left. During the following year the vision dropped to 2/60 in the right eye but remained 20/20 with a correction for hyperopia in the left eye. In December 1936 a cataract was removed from the right eye by a modified Verhoeff method, and a final visual result of 20/20 was obtained. His vision in the left eye remained about the same, now being 20/30 with a hyperopic correction.

Examination of the cardiovascular system in April 1938 showed the heart to be of normal size and shape, as revealed by a roentgenogram. The aorta was somewhat widened. The first sound was muffled and indistinct. The second was fairly well heard. There were no murmurs. The pulmonic second sound was greater than the aortic. The peripheral vessels showed no definite evidence of sclerosis. The blood pressure was 108 systolic and 74 diastolic. The electrocardiogram showed a PR interval of 0.26 second and a QRS spread of 0.14 second, with the form of a left bundle branch block.

On examination of the neuromuscular system in September 1937 the temporal muscles were shown to be somewhat atrophic, and the periorbital muscles, the orbicularis oris and the cheek muscles all very weak, the typical myopathic facies being produced. The patient cannot open his mouth widely. The sternocleidomastoid muscles are markedly atrophied. The deltoid, the muscles of the infrascapular and suprascapular fossae and the triceps are weak and somewhat atrophied. The biceps on each side and the pectoral muscles are of fairly good strength. Both the flexors and extensors of the forearm are markedly atrophied. The small muscles of the hand, including the interossei, are atrophied. Dorsiflexion of both feet is weak. The muscles of the thenar eminence show active myotonia. Mechanical myotonia is obtained in the thenar and hypothenar groups of muscles, the calf muscles and the glutei. Electrical testing shows a typical myotonic reaction in the thenar and hypothenar muscle groups. The biceps, abdominal and patellar reflexes are present. The achilles tendon reflexes were not obtained. Chvostek's sign is absent.

The results of the Wassermann and the Eagle flocculation test were negative. Several examinations of the urine and blood counts gave normal results. The basal metabolic rate in January 1936 was —16 per cent, and in July 1936 it was —20 per cent. The calcium and phosphorus (inorganic) contents of the serum as determined on several different occasions was as follows (in milligrams per hundred cubic centimeters): Jan. 20, 1936, calcium 9.2, phosphorus 3.9; July 20, 1936, calcium 10.6, phosphorus not determined; July 21, 1936, calcium 10.0,

phosphorus 5.4; July 25, 1936, calcium 11.1, phosphorus not determined; Nov. 22, 1937, calcium 9.0, phosphorus 3.0. On July 20, 1936, the cholesterol content of the blood was 154 mg. per hundred cubic centimeters, and the chloride content (as sodium chloride) was 522 mg. per hundred cubic centimeters.

The moist weight of the lens removed in December 1936 was 0.1823 Gm. The lens was immediately ground up with sodium sulfate, dried for twenty-four hours in an incubator and then extracted with chloroform. The cholesterol content of the lens was 1.12 mg. per hundred cubic centimeters, or 0.614 per cent of the moist weight of the lens.

Roentgenologic examination of the gastrointestinal tract in April 1938 revealed normal peristaltic waves in the esophagus; the stomach appeared to be of normal shape and position; a constant defect was seen in the pyloroduodenal region; the pylorus did not appear to be unusually patent; about one fifth of the barium sulfate meal remained in the stomach after six hours; the gallbladder and the appendix were not definitely visualized; there was some spasticity of the colon, but there was no definite roentgen evidence of organic disease.

CASE 13.—*Myotonia, atrophy, cataracts, baldness, basal metabolic rate —26 per cent.*

F. B., aged 44 years, was examined in April 1938. The patient's father died at 75 years of age in a state hospital to which he had been committed with a diagnosis of senile dementia. The patient said that his father wore glasses for many years and that for a number of years before his death his vision was so poor that he could not use a mirror to shave himself. The patient's mother was mildly diabetic and died at 81 years of age. One sister in her fifties had diabetes and, according to the patient, had difficulties with her eyes and legs. Another sister died in her fifties; she once told the patient that her hands "stuck to things." At the time this paper was written there were several other brothers and sisters whom we hope to examine in the future.

At about the age of 16 or 17 years, the patient first noticed that if he gripped an object strongly he would have difficulty letting go. This difficulty in relaxing his grip gradually became worse. At 22 to 23 years of age he noticed that his grip was not as strong as that of his fellow workers. Since that time there had been a gradual loss of strength in his grip, and in the last three years it was noticed that the weakness was marked. The strength in his arms and shoulders also decreased. He said that about two years ago people called his attention to the fact that he walked as though he had a "wooden leg or was paralyzed." Since that time he had been conscious of an increasing difficulty in walking. During the last year a stiffness of the ankles on starting to walk had been present. He had recently been tiring with very little exertion.

In the last six months his voice had become lower in pitch, less clear and somewhat husky. Occasionally he had difficulty in drinking water from a fountain.

His hands and feet had been cold as far back as he could remember. Print blurred when he read, and his eyes frequently burned and watered.

The patient had had mumps, with no associated orchitis. He had typhoid fever at 14 and pneumonia at 22 years of age. At the age of 30 years he was in the hospital with a pain in the right side, which was attributed to a ureteral stricture. He had gonorrhea at 22 years and again at 33 years of age; after the second attack he had some pains in the joints and swelling. He married at the age of 22 and has been divorced for about ten years. He has had no children, although he said his wife was pregnant on several occasions and induced abortions.

Physical examination in April 1938 of the patient revealed him to be a tall well nourished white man of 44 years. He is intelligent and cooperative. His voice is

definitely nasal, and his gait is of "steppage" nature. He is bald, with a graying rim of hair. Most of the teeth are present, although in poor condition. The thyroid is small but very firm. The results of examination of the lungs and abdomen were negative. Both testicles were possibly somewhat softer and smaller than normal.

The examination of the eyes showed a slight marginal blepharitis and a chronic conjunctivitis. Slit lamp examination after the introduction of homatropine hydrobromide showed many fine opacities, varying in size from that of a dust particle to almost a millimeter in diameter. The opacities were scattered throughout the cortex of the lens, extending well into the central area. They were a grayish white, but refractile, and appeared blue and blue-green at times. The fetal nucleus was not involved. Vision with glasses was 20/20 in both eyes.

The heart and aorta were normal, as shown by roentgenologic examination (April 1938). The blood pressure was 96 systolic and 64 diastolic with the patient in the recumbent position and 104 systolic and 72 diastolic when he was in the sitting position. The systolic pressure fell about 10 mm. with deep inspiration. The heart sounds were somewhat faint but normal in character. The aortic second and the pulmonic second sound were of about equal intensity. No murmurs were heard. Peripheral sclerosis was not evident. The electrocardiogram (April 1938) was normal except for a somewhat high take-off of the ST segment in lead I (1 mm.) and in lead II (1 mm.).

The temporal muscles were markedly atrophied, and the masseter muscles were somewhat atrophied. The periorbital muscles and the orbicularis oris were weak. The sternocleidomastoids were almost completely atrophied. The muscles of the supraclavicular fossae and the deltoids were somewhat atrophied. The biceps and especially the triceps on each side were weak and somewhat atrophic. Both the flexor and the extensor muscles in the forearm were very weak and atrophic. The muscles of the thenar and hypothenar eminences were only slightly involved, but the interossei were definitely atrophied. Flexion and extension of the thigh were fairly good, as was extension of the knees. Flexion of the knees was weakened. Plantar flexion of the feet was fair on the left and weak on the right. Dorsiflexion of the feet was markedly weakened. Voluntary myotonia was present in the movements of the fingers and thumbs and in the ankle movements. Mechanical irritability of the muscles was increased in most regions. Mechanical myotonia was present in the tongue, chin muscles, deltoids, biceps and triceps on each side, the flexors and extensors in the forearm, the muscles of the thenar and hypothenar eminences, the quadriceps on each side and the left gastrocnemius. The patellar and the abdominal reflexes were present and normal. The biceps and achilles tendon reflexes could not be obtained. Chvostek's sign was positive. Trousseau's sign was negative.

The results of the Wassermann and the Eagle test were normal. Examination of the spinal fluid gave normal results. On April 25, 1938 the calcium content of the blood serum was 9.3 mg. per hundred cubic centimeters, and the phosphorus content was 2.8 mg. The basal metabolic rate was —26 per cent, and the cholesterol content of the blood was 148 mg. per hundred cubic centimeters.

Important features of dystrophia myotonica brought out by the foregoing case histories will be discussed in the following order: (1) hereditary features, (2) onset, (3) myotonia, (4) atrophy, (5) cataracts, (6) endocrine and metabolic changes, (7) mental changes, (8) cardiovascular system and (9) gastrointestinal system.

HEREDITARY FEATURES

The hereditary features of dystrophia myotonica are of the greatest importance, because they throw much light on the nature of the disease and help to differentiate it from other heredofamilial disorders of the neuromuscular system as well as from the more closely related hereditary disorder myotonia congenita (Thomsen's disease). Fleischer,[7] Henke and Seeger[8] and others who have studied the heredity of this disease, including two of us (A. R. and J. J. W.),[9] have stated the belief that it is transmitted as a dominant. Unlike such a character, however, the determiner for dystrophia myotonica may apparently be present without manifesting itself, as indicated by the frequency with which the parents of our patients appeared to be normal and by the occurrence of isolated cases of dystrophia myotonica which can be traced back several generations to a common ancestor. Although dominant genes need not affect every generation, the large number of unaffected parents is not to be explained solely in this manner. To clarify this apparent inconsistency, geneticists have utilized the concept of "progressive inheritance." In diseases which exhibit progressive inheritance, the onset of the disease is at an earlier age in successive generations (anticipation). The disease also may become increasingly severe in successive generations (potentiation). In the light of this concept one may interpret the inheritance of dystrophia myotonica as follows: It is due to a dominant mutation which is at first manifested by very few signs, because of the mildness of the condition or because the patients do not live long enough to show many of the signs. In successive generations the disease sets in at an earlier age and increases gradually in severity until, finally, the full-blown syndrome of dystrophia myotonica can be recognized.

This interpretation of the course of events receives important confirmation from two sources. The first is the common occurrence of cataract, one of the most important signs of the disease, in the generations preceding the definitely dystrophic generation. Fleischer has shown that the occurrence of this cataract presents also the remarkable phenomenon of anticipation; that is, the age of onset is earlier in each succeeding generation. In antecedent generations occur senile cataracts; in later generations, presenile cataracts; in the definitely dystrophic generation the cataracts may occur in youth. The second source is the earlier age of onset of the disease in the dystrophic children of

8. Henke, K., and Seeger, S.: Ueber die Vererbung der myotonischen Dystrophie: Genetischer Beitrag zum Problem der Degeneration, Ztschr. f. d. ges. Anat. (Abt. 2) **13**:371, 1927.

9. Ravin, A., and Waring, J. J.: Studies in Dystrophia Myotonica: I. Hereditary Aspects, Am. J. M. Sc. **197**:593, 1939.

dystrophic parents. By fairly exhaustive investigation of the literature, 32 instances were found in which both parents and children were affected; in every one of these, the age of onset of the disease in the children was at an earlier age than in the parents.

The foregoing interpretation may be summarized as follows: The disease appears to be due to a dominant factor which is at first manifested by no signs or by very slight signs, notably cataract. In those families in which cataract occurs, its onset at an earlier age in succeeding generations is evidence of the defective gene. Finally, in one generation the complete syndrome of dystrophia myotonica appears. Persons with the disease now transmit it to their children as a simple dominant. The onset of the disease in the children is at an earlier age than in the parents, until finally a generation occurs in which the onset is before maturity, and the disease ceases to appear in that family.

It seems probable that the defective gene appears first in a family by mutation. One may conclude with McFarland and Meade [10] that "the cause of mutation or suddenly appearing striking variation is unknown. It, or something comparable to it, may occasionally modify the germ plasm in such a manner as to result in congenital deformity, insanity, dyscrasia, metabolic disturbance or tumor. Once changed by mutation, the germ plasm may carry the newly acquired character through many generations or may end it with one generation, when it results in a state incompatible with the propagation of its abnormal kind."

ONSET

The onset of dystrophia myotonica has usually been stated to be in the third or fourth decade. From what has been said about the heredity of the disease it is evident, however, that the age of onset will vary markedly with the generation affected. The disease is likely to be first recognized in the generation in which the onset is in the third or fourth decade of life, because in the preceding generation the disease begins at a later age and only rarely progresses to a point where the diagnosis is made before death. The presence of cataract in one of the parents of a patient with dystrophia myotonica might in retrospect be considered as evidence that that parent had the disease, although the muscle symptoms had not progressed to the point where the diagnosis is made. The children of a person in whom the disease began in the third or fourth decade may show the disease in the second or even the first decade of life (cases 5 and 9).

10. McFarland, J., and Meade, T. S.: The Genetic Origin of Tumors Supported by Their Simultaneous and Symmetrical Occurrence in Homologous Twins, Am. J. M. Sc. **184**:66, 1932.

One of the most impressive features of the disease is the insidiousness of its onset and the slowness with which it progresses. From the patients' histories and from the observation of several patients over a period of more than three years, we feel that degenerative signs are present for many years before they attract the patient's attention. The apparent insensibility and indifference of these patients to their physical disabilities are undoubtedly due in part to the insidious manner in which the disease develops. Since they are perhaps honestly unaware of the earliest muscular changes, the time of onset of the disease is apt to be underestimated by many years.

It is not possible in every instance to identify the initial symptom among the many dystrophic features of the disease. Usually one dystrophic feature appears either to have preceded the others or to have progressed more rapidly. From the histories of the patients of this series, myotonia appears to have been the first symptom in 5 patients, muscle weakness and atrophy in 4 patients and cataract in 3 patients; in 1 patient myotonia and atrophy began at the same time. It is possible, however, that myotonia may be, as many believe, the earliest symptom; but since it is not as disabling as the atrophy, the patient's attention is not attracted to it. Thus, the presenting complaint is usually the result of the muscular weakness, even when myotonia preceded the weakness by many years. The observation that in 2 of our patients cataract was present without the other symptoms having yet become of sufficient severity to be recognized would indicate that cataract is often the earliest evidence of the condition.

The sex incidence in the 5 patients presenting themselves for examination was 4 men and 1 woman. In the entire group of 13 patients, it was 8 men and 5 women. If to these 13 patients are added 5 patients who were not examined but who in our opinion, based on a study of the family histories, undoubtedly had the disease, the sex incidence becomes 10 men and 8 women. This is close to the 1 to 1 ratio expected on hereditary grounds.

MYOTONIA

After contraction, the myotonic muscle persists in a state of contraction, from which it relaxes slowly to resume its resting state, only after thirty seconds or more in some patients. The contraction persists after the stimulus producing it has ceased to act and appears, therefore, as a slowness or delay in relaxation. In contrast to myotonia congenita (Thomsen's disease), in which the myotonia is generalized and the only cause of disability, the myotonia in dystrophia myotonica is limited in distribution and overshadowed in importance by the progressive

muscular atrophy. The myotonia is, however, so characteristic that it deserves emphasis because of its great diagnostic value.

Myotonia occurs most commonly in the muscles of the forearms and hands, where it is manifested by an inability to relax promptly, easily, and naturally the hand clasp, to "let go" any object firmly grasped. One of our patients, a railroad brakeman, nearly lost his life because of his inability to "let go" the iron handle on a box-car. A younger patient could not relax his grip "frozen" to his golf club after a stroke. A carpenter after driving a few nails could not lay down his hammer. A housewife found pulling weeds a slow process because of an inability to "let go" a weed pulled with difficulty from the ground. Greenfield wrote of a physician with this malady who found himself under suspicion because of his suggestively caressing hand clasp when shaking hands with his women patients. Myotonia also occurs at times in the muscles of mastication, as indicated by a curious difficulty on starting to talk, chew or swallow, and in the muscles of the legs, as indicated by "stiffness" of the muscles and joints on starting to walk or run or get up from a cramped position.

When the muscular contraction is voluntary, as in the aforementioned instances, we have used the term "voluntary myotonia"; if the muscle is stimulated to contract by mechanical or electrical means we have used the terms "mechanical myotonia" and "electrical myotonia."

The prolonged contraction characteristic of myotonia is easily distinguished from simulating conditions by the following properties:

1. The difficulty in relaxing the contracted muscle becomes less with each repetition of the contraction, and after several contractions the relaxation occurs with apparently normal rapidity. The difficulty in relaxation is accordingly most evident after a period of rest. If the patient is instructed to open and close his fist repeatedly and as rapidly as possible, the first few movements are performed slowly and with difficulty, but with each repetition the movement becomes more facile, until it is carried out with apparent normal rapidity. If, however, the patient rests for a while, the difficulty returns.

2. Myotonia is not painful.

3. Myotonia increases in degree, up to a limit, with increase in the force of contraction. M. J. B. (case 9) could open and close her fist without noticeable difficulty, but after squeezing the dynamometer she could release it only with effort.

4. The contractions which show myotonia are voluntarily produced contractions. Involuntary contractions occur only rarely in diseases associated with myotonia and then represent an accidental association.

Voluntary myotonia has been markedly decreased by the administration of quinine[3] and to a less extent by the administration of

epinephrine.[11] It has also been somewhat decreased by calcium, given intravenously.[11] The administration of insulin produced a decrease when symptoms of hypoglycemia were present, and it was probable that the decrease depended on the mobilization of epinephrine.[11] The administration of prostigmine aggravated myotonia, and the administration of potassium chloride has been reported to aggravate it.[12] Warmth usually decreases myotonia, and cold increases it. Possibly by increasing involuntarily the strength of contraction, excitement and fright increase myotonia.

Mechanical myotonia is most easily demonstrated by striking the muscle with a percussion hammer. In the case of large muscles, a lingering furrow or dimple is produced by the persistence of the contraction of the stimulated muscle fibers. Smaller muscles, such as those of the thenar and hypothenar eminences, may contract as a whole. Mechanical myotonia is usually more widespread than voluntary myotonia. Its presence in the tongue is especially constant and worthy of note. The muscles commonly involved are listed in table 1.

The response of myotonic muscles to electrical stimulation is very characteristic. The essential feature is the persistence of the contraction after cessation of the stimulating current, but the details of the response of the muscles and nerves to faradic and galvanic currents are too complex for the present discussion. The typical myotonic response is complicated by the presence of atrophy in many of the muscles. The total reaction of the muscle to mechanical and electrical stimulation was called by Erb [13] the "myotonic reaction."

ATROPHY

The atrophy is characterized by a typical pattern of involvement, which includes the muscles of the face, the sternocleidomastoids, the muscles of the forearm, the quadriceps and the dorsiflexors of the foot. The muscles in one or more of these locations usually show the initial involvement, but when the condition is moderately advanced the entire group is more or less affected. Atrophy may affect muscles which are or have been myotonic, or it may affect muscles which apparently have shown no myotonia.

In the face, the muscular involvement results in the so-called myopathic facies, consisting of temporal hollows, sunken and sagging cheeks, drooping mouth corners and a persistently glum expression. The orbicularis oculi of each side, the orbicularis oris and the temporal muscles are early affected. Atrophy and weakness of the pharyngeal

11. Ravin, A.: Studies in Dystrophia Myotonica: III. Experimental Studies in Myotonia, Arch. Neurol. & Psychiat. **43**:649 (April) 1940.

12. Russell, W. R., and Stedman, E.: Observations on Myotonia, Lancet **2**: 742, 1936. Kennedy and Wolf.[3a]

13. Erb, W. H.: Die Thomsen'sche Krankheit, Leipzig, F. C. W. Vogel, 1886.

Case number	1	2	3	4	5	6	7	8	9	10	11	12	13
Patient	O. M.	N. M.	J. L.	C. M.	H. M.	J. B.	M. W. B.	R. B.	M. J. B.	J. M.	S. E.	N. P.	F. B.
Age and sex	43, M	59, F	56, F	58, M	22, M	60, M	62, M	27, M	20, F	40, F	35, F	54, M	44, M
Evidence of heredity	+	+	+	+	+	+	+	+	+	+	+	+	+
Probable age of onset													
Mytonia	33	52	45	48	..	?	57?	25	13	23	..	36	16
Atrophy	27	57	55	..	..	47	48?	18	?	35	..	36	22
Cataract	30	46	52	..	20	60	?	27	20	34	35	41	44
Active myotonia													
Hand grasp	+++	+	+	+?	0	+	+	+++	+	+++	0	+	+
Jaw	0	?	0	0	0	+?	0	0	0	0	0	+	0
Legs	+	0	0	0	0	+	+	+	0	+?	0	+	+
Mechanical myotonia													
Thenar	+++	+	++	0	+?	++	+	+++	++	++	0	++	++
Hypothenar	++	+	+	0	+?	+	+	++	+	+	0	+	++
Forearm, extensors	++	+	+	..	0	+	0	++	+	+	..	0	++
Forearm, flexors	0	0	Slight	..	0	0	0	++	+	0	..	0	+
Tongue	++	++	++	0	0	+	++	++	++	++	..	?	++
Gastrocnemius	..	0?	..	..	..	+	+?	+	+	+	..	+	+
Deltoid	+	0	0	..	?	+	0?	+	?	+	..	+?	+
Chin muscles	+	0?	0	..	..	+	+	+	+	+	..	+	+
Electrical myotonia—Muscles of thenar and hypothenar eminences	+	+	..	..	..	+	..	+	..	+	..	+	..
Atrophy or weakness													
Myopathic facies	++	+	?	0	0	+++	++	++	?	+++	0	++	+
Sternocleidomastoids	+++	+++	0	0	0	+++	+++	+++	+	+++	0	+++	+++
Forearms	+	+	+	0	0	+++	+++	+++	Slight	++	0	+++	++
Dorsiflexors of feet	+	++	0	0	0	+++	++	++	0	+	0	+	++
Temporalis muscles	++	Slight	0	0	0	++	+	+	+	++	0	+	++
Quadriceps	?	++	+	0	0	++	+	+	0	++	0	?	+
Biceps and triceps	?	0	0	0	0	++	+	+	+	++	0	+	++
General atrophy	0	0	0	0	0	++	+	+	0	Slight	0	0	Slight
Speech disturbance	?	0	0	0	0	++	+?	+	?	+	0	+	+
Gait disturbance	+	++	Slight	0	0	++	++	+	0	++	0	+	++
Cataract													
Right	+	+	+	0	+	+	+?	+	+	+	+	+	+
Left	+	+	+	0	+	+	+?	+	+	+	+	+	+
Baldness	+	0	0	Slight	0	+	+	0	0	0	0	+	+
Testicular atrophy	+?	..	..	..	0	+	+?	+	..	..	..	0	0?
Pain	0	0	+	0	0	0	0	0	0	+	0	0	0
Reflexes													
Patellar	++	++	++	+	+	++	0	+	++	0	..	+	+
Achilles tendon	+	0	..	..	..	0	..	+	++	0	..	0	0
Biceps	++	++	++	..	..	0	..	?	+	0	..	++	0
Babinski	0	0	..	..	..	0	..	0	0	0	..	0	0
Romberg	0	0	..	..	..	?	..	..	0	0	..	0	0
Thyroid tumor	+	+?	0	0	0	0	0	0	0	0	..	+	0
Basal metabolic rate	−37	−31	..	..	..	−19	..	−30	..	−10	..	−20	−26
Blood cholesterol (mg. per 100 cc.)	180	148	..	..	..	167	..	143	..	230	..	154	148
Chvostek's sign	0	0	0	..	..	0	0	0	0?	0	..	0	+
Trousseau's sign	0	0	..	..	..	0	..	0	0	0	..	0	0
Blood calcium/blood phosphorus (mg. per 100 cc.)	11.0/3.8	12.2/3.6	..	..	..	9.8/4.8	..	10.1/4.6	..	10.0/3.3	..	9.2/3.9	9.3/2.8
Blood group	II	II	..	..	..	IV	..	III	..	IV	..	IV	..
Color blindness	0	0	..	..	..	+	..	0	..	0	..	0	..
Height (inches)	73	66½	..	..	..	66½	..	67	..	68½	..	69	71½
Weight (pounds)	155	136½	..	..	..	98½	161	107	..	145	..	173	167

muscles also occur early and produce a nasal voice, poor enunciation and an easily fatiguing voice. The masseter muscles may be involved and with the weakened temporal muscles may result in a tendency to easy dislocation of the lower jaw. Atrophy of the tongue is late.

The involvement of the sternocleidomastoids is early and remarkably constant. In moderately advanced stages of the disease only a few fibers of the muscles may be present. The weakness is nicely demonstrated by asking the patient to sit up from the supine position. When the involvement is severe the head of the patient tends to fall back and is often supported with the hand.

The atrophy and weakness of the muscles in the forearms are especially incapacitating and frequently the presenting complaint. Of the flexor muscles, the superficial and deep flexors of the fingers and the long flexors of the thumbs are markedly involved. The flexors of the wrist show less involvement, and patients with this condition soon learn to depend on the wrists to lift objects. The extensor muscles are usually more markedly and universally affected than the flexor. The muscles of the thenar and hypothenar eminences do not show marked involvement until late, and the adduction and opposition of the thumb are therefore often strong after flexion of the fingers is almost gone. Since myotonia tends to disappear as the muscles atrophy, it may be evident in advanced stages of the disease only in the movement of the adduction and opposition of the thumb. In some patients the interosseus muscles are involved early. The hand tends to assume a position resembling a cone; the palm is contracted, and the fingers are bent at the metacarpophalangeal joints, with their tips coming together to form the apex of the cone.

In the lower extremities, the dorsiflexors of the foot are early affected, with the production of a foot drop and a steppage gait. When the quadriceps femoris becomes weak, the difficulty in walking is great. The patient is unable to raise the leg high enough to overcome the foot drop, and the risk of falling is great.

As the disease progresses, other muscles become weak and atrophied. In the far advanced conditions, most of the muscles of the body are involved, and the patient is markedly emaciated.

The atrophy is not associated with fibrillary twitching. The tendon reflexes are not abnormal but disappear as the muscles atrophy. At times the weakness and atrophy of the muscles of the lower extremities, especially in the early stages, are associated with pain, usually described as aching. Although Maas [14] in a recent report stated that the vibratory sense was found diminished in many persons with dystrophia myotonica, sensory disturbances are otherwise lacking.

14. Maas, O.: Disturbances of Sensibility in Dystrophia Myotonica, Brain **61**:449, 1938.

CATARACTS

Of the 13 patients in our series, 12 had cataracts. The 1 patient who did not appear by slit lamp examination to have cataracts had such slight evidence of the disease that it was only on the basis of the family history that the diagnosis could be made. Two patients, furthermore, had cataracts without any definite muscle changes. It may be concluded, therefore, that the presence of cataracts on slit lamp examination is one of the earliest and most constant features of dystrophia myotonica. The importance of the occurrence of cataracts in the ancestors of patients has already been emphasized.

On slit lamp examination of the lens, the characteristic observations are as follows: 1. Small regular opacities are found in the cortex of the lens, especially under the capsule. These opacities are highly refractile, appearing blue, blue-green and yellow. 2. A posterior subcapsular star-shaped opacity may be present very early, although no patient in our series had such a lesion before the punctate opacities were demonstrable. This is an opacity similar to that found in other forms of complicated cataract. 3. The cataracts develop very slowly, taking ten to twenty years to mature. The mature cataract, the punctate opacities having become confluent, is indistinguishable from other types of mature cataracts.

Although the cataract in its early stages almost always shows the changes just described, a diagnosis of dystrophia myotonica cannot be established on the evidence of the lenticular changes alone, as tetany, among other conditions, may produce somewhat similar changes. Several cataracts not unlike this type have been seen in patients in whom no etiologic factor could be established. Although the diagnosis of dystrophia myotonica cannot be made on the lenticular changes alone, it is evident that if a typical cataract is found in a person with a family history of dystrophia myotonica, that person has dystrophia myotonica as surely as his brother or sister who shows only muscular changes.

The cholesterol content of the lens removed from N. P. (case 12), by the intracapsular method, was 0.614 per cent of the moist weight. This is well within the limits for cholesterol content in lenses with mature cataracts of all types, as found by Salit and O'Brien,[15] namely 0.239 to 0.679 per cent, with an average of 0.512 per cent.

A chronic ulcerative type of blepharitis and chronic conjunctivitis was present in 9 patients and absent only in the 4 patients showing the least degenerative change. This rather constant observation has been mentioned only occasionally in other reports.

15. Salit, P. W., and O'Brien, C. S.: Cholesterol Content of Cataractous Human Lenses, Arch. Ophth. **13**:227 (Feb.) 1935.

ENDOCRINE AND METABOLIC CHANGES

The endocrine system of the body shows evidences of generalized and often marked involvement. Testicular atrophy is frequent (in 3 of the 8 men in this series), and when marked it results in impotence and infertility. Involvement of the ovaries is indicated by the frequent occurrence of menstrual irregularities and the marked infertility of women with the disease. The thyroid is often enlarged and of increased firmness. The basal metabolic rate is usually low; in the 7 patients of this series for whom estimations were made, it ranged from — 11 per cent to — 41 per cent with an average of — 25 per cent. The cholesterol content of the blood, on the other hand, was normal in every instance in which it was determined.

The resemblance of myotonia to tetany, the frequently reported presence of Chvostek's sign and even of Trousseau's sign and the almost invariable presence of cataract have suggested to many a hypofunction of the parathyroid glands. Against a hypofunction of the parathyroids may be mentioned the following facts: 1. Even superficial comparison of myotonia and tetany suffices to show that they are in no way related. In contrast to tetany, which is frequently painful, occurs spontaneously and is localized mainly in the extremities in the same pattern, myotonia is not painful, occurs always in connection with certain voluntary movements and cannot be produced by pressure on the nerve trunk or large vessels. 2. The calcium and phosphorus values in the blood are practically always normal, as they were in this series. 3. It is our feeling that what has usually been reported as Chvostek's sign is really produced by the direct stimulation of the hyperirritable facial muscles, rather than by a stimulation of a hyperirritable nerve. The former phenomenon was observed in several patients, but in only 1 patient was a true Chvostek sign obtained. Trousseau's sign was not obtained in any patient.

The conception of the pituitary as the master regulator of the endocrine system leads to the suggestion of a primary hypofunction of the pituitary as the fundamental cause of many of the changes. The low basal metabolic rate, the testicular and ovarian dysfunction, the general body emaciation and the alopecia observed in this series lend some plausibility to this suggestion.

Sugar tolerance tests on many of our patients failed to reveal the presence of any abnormality of carbohydrate metabolism. This work will be reported later.

Many studies of creatine excretion in myotonia congenita and dystrophia myotonica have failed to show any connection between the myotonia and creatine excretion. Abnormal creatinuria may be present when the muscle wasting is marked, but it is less than that seen in pro-

gressive muscular dystrophy.[16] Studies on creatinine and creatinine excretion in 3 of the aforementioned patients also will be reported later.

MENTAL CHANGES

Maas and Paterson [17] examined psychiatrically 29 patients with dystrophia myotonica. They found 17 of them to be of low intelligence, 11 on a congenital basis and 6 as a result of deterioration. They also found 6 patients who presented clinical pictures in some respects resembling classic syndromes of mental disorder. They felt that marked muscular wasting was associated with mental changes. A definite temperament was found by them in so many patients as to seem almost characteristic of the disease. It consisted in persistent and almost morbid cheerfulness, mild grandiosity and a lack of drive and initiative.

Our experience does not parallel that of Maas and Paterson. Whether it is as the result of hereditary defects or as the result of injurious prenatal and postnatal influences, a large percentage of mental defectives is found in many affected families. In other families, however, mental defects appear to be slight or absent. This was true in most of our cases. A careful study of our patients for the presence of mental deterioration is in progress and will be reported later. The characteristic temperament which Maas and Paterson described occurred infrequently, and those changes in temperament which were found seemed more of a reaction to body defects than the result of any special congenital or degenerative mental change.

CARDIOVASCULAR SYSTEM

Guillain and Rouquès [18] and d'Antona [19] have called attention to the high percentage of cardiovascular abnormalities in the small series of patients with dystrophia myotonica in whom the cardiovascular system has been adequately studied. These authors suggested the possibility that the cardiovascular system was also involved in the dystrophic process but cautiously stated that no conclusion must be drawn until

16. Milhorat, A. T., and Wolff, H. G.: Studies in Diseases of Muscle: V. Metabolism of Creatine and Creatinine in Myotonia Congenita, Myotonia Atrophica, Amyotonia Congenita, Dystonia Musculorum Deformans and Paralysis Agitans, Arch. Neurol. & Psychiat. **40**:680 (Oct.) 1938.

17. Maas, O., and Paterson, A. S.: Mental Changes in Families Affected by Dystrophia Myotonica, Lancet **1**:21, 1937.

18. Guillain, G., and Rouquès, L.: Le cœur dans la myotonie atrophique, Ann. de méd. **31**:158, 1932.

19. d'Antona, L.: Osservazioni sullo stato dell'apparato circolatorio e digerente nella distrofia miotonica: La sindrome endocrina ed umorale, Minerva med. **1**:833, 1935.

a larger series of cases have been studied. The abnormalities which have been noted by various workers include the following: hypotension, bradycardia, peripheral vasomotor disturbances, fluoroscopic and roentgenographic abnormalities and abnormalities of the electrocardiogram.

A large percentage of patients with dystrophia myotonica have blood pressures somewhat lower than average, and our impression from the reading of many case reports has been that hypertension is rare. In our series 5 patients (cases 1, 6, 8, 12 and 12), all with fairly advanced dystrophia myotonica, had what might be considered hypotension. Two patients (cases 5 and 9), not seriously affected, had low, but possibly average, blood pressures. Two other patients with marked involvement had blood pressures which might be considered low for their age, M. W. B. (case 7) 120 systolic and 78 diastolic at 62 years of age and J. M. (case 10) 116 systolic and 80 diastolic at 44 years of age.

The presence of bradycardia, which has often been observed and reported by others, is evident on examination of table 2.

Most of our patients complained of cold hands and cold feet and showed a more or less marked degree of cyanosis of the hands under the influence of mild cold.

None of the patients in this series had roentgen evidence of an enlarged heart, and except for some widening of the aorta in N. P. (case 12) no abnormality was found in the roentgenograms of the chest. This corresponds to the lack of significant changes in the size or shape of the heart found by most observers.

On auscultation, the heart except in 2 patients seemed normal. In our series a systolic murmur was heard in J. B. and M. J. B. (cases 6 and 9). In M. J. B. (case 9) the nature of the murmur and the absence of a rheumatic history suggested the possibility of a congenital heart lesion.

The percentage of our patients showing electrocardiographic abnormalities is surprisingly large and agrees in this respect with the observations of Guillian and Rouquès. Electrocardiograms were taken of 8 patients: Two patients (cases 6 and 9) were definitely normal; 1 patient (case 13) was normal except for a slightly high take off of the ST segments in lead I (1 mm.) and lead II (1 mm.); R. B. (case 8) showed a slight left axis deviation, and N. M. (case 2) showed a more marked left axis deviation; O. M. (case 1) had a low voltage and a PR interval of 0.23 second; N. P. (case 12) had a PR interval of 0.26 second and a left bundle branch block; J. M. (case 10) during the period of observation showed definite evidence of a myocardial infarction.

The large number of patients who showed abnormalities in the electrocardiogram is even more surprising when it is remembered that

hypotension was observed to be common and that peripheral sclerosis was slight in most patients. Nevertheless, the type of change observed would suggest coronary sclerosis rather than a dystrophic process involving the myocardium.

TABLE 2.—*Summary of Cardiovascular Examinations*

Case	Age	Severity of Disease	Blood Pressure	Pulse During B. M. R.	Results of Examination	Evidence of Peripheral Sclerosis	Cold Cyanotic Hands	Electrocardiograms
1	43	++	100/68	56	Normal on roentgen examination and auscultation	0	+	Low voltage of P waves; PR = 0.24 sec.; low voltage of QRS waves, largest excursion 5 mm.
2	59	++	138/90	70	Normal on roentgen examination and auscultation	?	+	PR = 0.20; moderate left axis deviation
3	56	+	122/80	80*	Normal on percussion and auscultation	0	+	Not done
4	53	Slight	130/80	..	Normal on percussion and auscultation	0	0	Not done
5	22	Slight	108/68	..	Normal on percussion and auscultation	0	0	Not done
6	60	++++	104/70	72	Normal on roentgen examination; rough, loud systolic murmur at apex	Slight	+	Normal ekg.
7	62	+++	120/78	92*	Normal on percussion and auscultation	?	+	Not done
8	27	++	100/80	49	Normal on roentgen examination and auscultation	0	+	PR = 0.20; slight left axis deviation
9	20	+	106/70	..	Normal on roentgen examination; systolic murmur, loudest in pulmonic area	0	+	Tendency to right axis deviation
10	46	+++	116/80	58	Normal on roentgen examination and auscultation	0	+	Evidence of coronary changes
12	54	+++	108/74	50	Aorta somewhat widened on roentgen examination; indistinct first heart sound	+	+	PR = 0.26 seconds; left bundle branch block
13	44	++	96/64	60	Normal on roentgen examination and auscultation	0	+	Slightly high take off of ST segment in lead I (1 mm.) and lead II (1 mm.)

* Not during determination of the basal metabolic rate.

GASTROINTESTINAL TRACT

d'Antona [19] reported that fluoroscopic examination of the gastrointestinal tract in 1 patient suggested the occurrence of myotonic phenomena in the esophagus and possibly in the stomach. We did not observe a similar phenomenon in any of the 7 patients in this series who had roentgenographic and fluoroscopic examinations of the gastrointestinal system.

DIAGNOSIS

The disease must be differentiated from myotonia congenita (Thomsen's disease), from the various progressive muscular atrophies and dystrophies, from other diseases producing presenile cataracts and from various endocrine disorders.

The hereditary nature of the disease is of the greatest diagnostic importance; atrophy occurs in a typical pattern; myotonia is characteristically limited in distribution; cataract occurs at an early or middle age; associated testicular atrophy is most significant, and finally, a low basal metabolic rate is commonly present.

TREATMENT

It is one of the distinguishing features of the heredodegenerative diseases, of which dystrophia myotonica is a member, that they increase slowly and inexorably in severity. The insidiousness with which the disease sets in and the slowness with which it progresses have been described. The progression of the disease is almost imperceptible to close friends and relatives. It is this slowness of progression which makes evaluation of any treatment most difficult. Treatment which merely halted the progression of the disease would have to be used for many months or years before one could be sure of its effect. Only if the drug produced a dramatic change in the patient's condition could one be sure of a beneficial therapeutic effect. The possibility of the spontaneous occurrence of periods during which the progression of the disease stops or during which even improvement may occur further complicates the evaluation of treatment.

The type of change, degeneration, makes treatment exceedingly difficult. The greatest benefit obviously could be obtained by prevention—by voluntary celibacy of members of affected families or by voluntary contraception! After the degenerative changes are present, little can be expected from treatment. An atrophied muscle or an atrophic testicle cannot be replaced, nor a clouded lens cleared!

Treatment is further complicated by the number of tissues affected. If the widespread involvement is due to the absence of one specific substance, a hormone for example, the ideal treatment would be substitution therapy. Although it is possible that all changes may be due to a single deficiency, positive evidence as to its nature is lacking. In the absence, therefore, of specific substitution therapy, the symptoms must be treated individually.

MYOTONIA

Treatment of the myotonia is discussed first, because it has been the most satisfactory. In 1936 Wolf [8c] reported the great improvement in myotonia produced by quinine. This observation has since been amply confirmed. Given by mouth, in doses of 15 to 30 grains (0.97

to 1.94 Gm.) daily, quinine temporarily abolishes almost all evidence of the myotonia. Quinine has not been shown, however, to have any effect on the muscular weakness and atrophy. Since patients with dystrophia myotonica, unlike patients with myotonia congenita, are not especially incapacitated by their myotonia and usually seek medical advice because of muscle atrophy or cataract, quinine generally does little to correct the original complaint. Thus, of the 6 patients receiving quinine (O. M. [case 1] 10 to 20 grains [0.65 to 1.29 Gm.] daily for two months, N. M. [case 2] 10 grains [0.65 Gm.] daily for five weeks, J. B. [case 6] 15 grains [0.97 Gm.] daily for four weeks, R. B. [case 8] 5 grains [0.32 Gm.] three times daily for one month, J. M. [case 10] 10 to 20 grains [0.65 to 1.29 Gm.] daily for over thirteen and a half months, N. P. [case 12] 10 to 15 grains [0.65 to 0.95 Gm.] daily for ten months), only J. M. (case 10), who had a marked myotonia of the hands with only moderate atrophy, felt enough improved to desire continuation of the quinine. Her difficulty in walking, however, showed little if any change under quinine therapy. These results are similar to those obtained by Kennedy and Wolf.[3a] Unlike the patients of Kennedy and Wolf, our patients complained of gastric distress on taking much more than 15 to 20 grains (0.97 to 1.29 Gm.) of quinine sulfate a day.

The effect of epinephrine and calcium on myotonia is too evanescent to make these drugs of value for the treatment of myotonia.

ATROPHY

The muscular atrophy is usually the most important disabling feature and at the same time the one least amenable to treatment.

The value of aminoacetic acid in the treatment of progressive muscular dystrophy has been reported by many workers.[20] Its use in dystrophia myotonica has been limited. Slauck [21] found no effect from the use of aminoacetic acid by itself but great improvement from aminoacetic acid and testicular extract (see "Testosterone Propionate"). Three patients in this series were given aminoacetic acid over fairly prolonged periods, J. M. (case 10) 30 Gm. daily for eight months, N. P. (case 12) about 20 Gm. daily for six months, and R. B. (case 8) about 20 Gm. daily for one month by itself, for one month with anterior pituitary extract and for two months with testosterone propionate. N. P.

20. Harris, M. M., and Brand, E.: Metabolic and Therapeutic Studies in Myopathies, with Special Reference to Glycine Administration, J. A. M. A. **101:** 1047 (Sept. 30) 1933. Tripoli, C. J., and Beard, H. H.: Muscular Dystrophy and Atrophy: Clinical and Biochemical Results Following the Oral Administration of Amino-Acids, Arch. Int. Med. **53:**435 (March) 1934.

21. Slauck, A.: Die therapeutische Beeinflussbarkeit der Dystrophia myotonica, zugleich ein Beitrag zur Kenntnis vom intermediären Stoffwechsel des Muskels, Verhandl. d. deutsch. Gesellsch. f. inn. Med., Kong. 45, 1933, p. 175.

(case 12), who believed himself improved with every type of treatment but in whom objective evidences of improvement could not be seen, thought himself improved after administration of aminoacetic acid. J. M. (case 10) at first said that she was improved but near the completion of her period of treatment with aminoacetic acid thought she was no better than she had been at the beginning of the treatment. Her husband and many of her neighbors thought she was improved. It is quite possible that the progression of the disease was halted. Objectively some improvement appeared to occur during the first few months but none during the last months. R. B. (case 8) took aminoacetic acid alone over too short a period to evaluate its effect.

Anterior Pituitary Extract.—This extract was given because of the widespread nature of the involvement in dystrophia myotonica and the correspondingly large number of regulatory actions which have recently been attributed to the pituitary gland. The most striking improvement obtained in any of the patients with any drug was obtained with anterior pituitary extract (Squibb) in J. B. (case 6). He was given 2 cc. of extract three times weekly for a period of about ten months. During the first five months he gained 12 pounds (5.4 Kg.) in weight, felt stronger and better than he had for years, went out and tried to do some work, no longer had as much difficulty as he had previously in opening doors, and felt happy and encouraged. He walked somewhat better than before treatment. No change was evident in the myotonia. During the last five months of treatment he felt he was no longer gaining, and he stopped the treatment. Seen a year after starting treatment, he appeared somewhat better than he had been on starting treatment.

N. P. (case 12) received 2 cc. of the drug three times weekly for four months. As with all other drugs used, the patient believed himself improved, but objective evidence of improvement was lacking, and during the period of treatment he became conscious of a stiffness of his legs in the morning which he had not noticed previously.

R. B. (case 8) received 2 cc. of anterior pituitary extract three times weekly along with 20 to 30 Gm. of aminoacetic acid for a month. Subjective and objective evidences of improvement were questionable.

Testosterone Propionate.[22]—This drug was used for the following reasons:

1. Slauck [21] had reported improvement in the muscular atrophy of dystrophia myotonica by the combined use of aminoacetic acid and a testicular extract (erugon).

2. Testicular atrophy occurred in many of these patients.

22. The testosterone propionate used in this study was furnished by the Schering Corporation and the Ciba Pharmaceutical Products, Inc.

3. Papanicolaou and Falk [23] reported that general musclar hypertrophy could be induced in guinea pigs with the androgen.

N. P. (case 12) received 10 mg. of testosterone propionate three times weekly for one month and then 25 mg. three times weekly for six months. There was no evidence of improvement, and during this period the patient complained of a weakness of the right arm, most evident during shaving. This patient had no testicular atrophy. He said his sexual desire was normal and was not affected by the medication.

O. M. (case 1) received 25 mg. of testosterone propionate twice weekly for six months. The patient, who would probably deny improvement if it did occur, was not sure that he had improved, but his wife thought he was better. That he continued to come for treatment is some evidence, considering his peculiar nature, that he may have been somewhat benefited. His testicles appeared to be atrophic, and he said that he had lost all desire for intercourse and that the testosterone produced no change in his desire, although here again he would probably conceal any change.

R. B. (case 8) received aminoacetic acid (15 to 30 Gm. daily) and testosterone propionate (10 mg. daily) for six weeks; then he received testosterone propionate by itself (10 mg. daily for one month and 25 mg. three times weekly for two months). He was not seen at the conclusion of this treatment, but he thought that he was benefited by the therapy. His sister believes that now, one year after treatment was begun, his hands are stronger than they were previously. The fibrillary twitchings described by Slauck as occurring during administration of the combination of aminoacetic acid and testicular extract and the dramatic improvement which he apparently obtained were not seen in this patient.

F. B. (case 13) received too few injections of testosterone propionate for him to notice any effect on muscle strength, but he did complain of excessive erections.

Epinephrine and an Epinephrine-Pilocarpine Mixture.—Because of the improvement which it produced in the myotonia, epinephrine was given to observe its effect on muscle strength. The epinephrine-pilocarpine mixture (one part of a 1 per cent solution of pilocarpine hydrochloride and two parts of a 1 to 1,000 solution of epinephrine hydrochloride solution) was used because of the improvement which it has been reported to produce in progressive muscle dystrophy.[24]

23. Papanicolaou, G. N., and Falk, E. A.: General Muscular Hypertrophy Induced by Androgenic Hormone, Science **87**:238, 1938.

24. Hough, G. de N., Jr.: Progressive Pseudohypertrophic Muscular Dystrophy: Results of Treatment with Epinephrine and Pilocarpine, J. A. M. A. **101**:2113 (Dec. 30) 1933.

N. M. (case 2) was given 8 to 11 minims (0.49 to 0.67 cc.) of epinephrine subcutaneously twice weekly for four months. She felt benefited, and her family told her that she walked better. Objectively, improvement, although not marked, did appear to be present. She was then given a course of fifty injections of 0.3 cc. of the epinephrine-pilocarpine mixture (three times weekly). Again the patient believed that she was definitely improved, and it is true that at the time of writing, over a year after she began the treatment, she appears to be no worse and possibly somewhat improved.

J. B. (case 6) received several injections of epinephrine and appeared definitely improved. The improvement was especially noticeable in an increased ability to open doors.

Ephedrine Sulfate.—J. M. (case 10) and N. P. (case 12) both received ⅜ grain (0.025 Gm.) of ephedrine sulfate for several weeks. They were also receiving aminoacetic acid at the same time, and any change due to the ephedrine could not be determined.

Thyroid.—O. M. (case 1) received 5 to 10 grains (0.32 to 0.65 Gm.) of thyroid for a period of over two years. He said that he noticed no improvement from it, but according to the records of the physician who gave it to him, the mental and physical lethargy of this patient were markedly decreased by the treatment.

CATARACT

The cataract associated with dystrophia myotonica is adequately treated by operation. The usual type of cataract extraction used in treating patients with senile cataract is also suitable in the treatment of dystrophia myotonica. The operation should be left to the judgment of the surgeon. In our series 1 patient had combined extractions, with a visual result of 20/20 with the proper correcting lens. In another, the extraction was intracapsular, by a modified Verhoeff method, with an equally satisfactory result. No contraindication exists to operation, as there is no evidence of other intraocular pathologic change.

SUMMARY OF TREATMENT

The myotonia can be adequately treated by quinine in these patients, but the quinine does not influence the muscular weakness and atrophy, which produce the greatest disability. Of the many medications used for their effect on the weakness and atrophy, the greatest improvement resulted from anterior pituitary extract in J. B. (case 6), but anterior pituitary extract produced little if any effect in 2 other patients. Aminoacetic acid, epinephrine and epinephrine with pilocarpine were believed by the patients to have been beneficial, although objective signs of

improvement were not so evident. These drugs may have prevented a progression of the condition. Testosterone propionate was of questionable value. The benefits of ephedrine sulfate cannot be appraised from our limited experience with it. Thyroid has not been given sufficient trial for its effect in overcoming some of the symptoms of hypometabolism which these patients showed.

SUMMARY

A detailed study of 13 patients with dystrophia myotonica is presented. A description of the type of heredity is given, and the conclusion is drawn that the disease is transmitted as a single dominant factor modified by "progressive inheritance." The characteristics of myotonia which distinguish it from simulating conditions are described. The typical pattern of the muscular atrophy is emphasized. The rather typical cataract is believed to be one of the earliest and most constant changes. Various endocrine and metabolic changes which form part of the picture of the disease are described. Mental changes in this group of patients did not appear to be important or characteristic. It is shown in this series, as in some previously reported, that the incidence of cardiovascular changes as indicated by electrocardiographic observations is surprisingly high. Radiologic studies of the gastrointestinal tract revealed nothing of significance. The results of treatment with quinine, aminoacetic acid, anterior pituitary extract, testosterone propionate, epinephrine and epinephrine-pilocarpine mixture and ephedrine sulfate are reported.

Drs. L. E. Daniels and J. P. Hilton, of the neurologic service, referred to us J. B. (case 6), N. P. (case 12) and S. B. (case 13); Drs. E. A. Schmidt and R. R. Anderson made the fluoroscopic and roentgenographic studies; Dr. R. C. Lewis, professor of biochemistry, University of Colorado School of Medicine, and members of his department made the determination of the cholesterol content of the lens removed from N. P. (case 12) and also the many determinations of the blood chemistry and of the basal metabolic rate.

THE FORMATION OF URINE

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The formation of urine is the result of the simultaneous occurrence of three processes, only one of which is explicable in terms of known forces. These processes are: (1) glomerular filtration, or the passage of a colloid-free filtrate of blood plasma through the glomerular capillary endothelium and its investing squamous epithelium owing to an excess of hydrostatic over colloid osmotic pressure; (2) tubular excretion, or the passage of solutes from the plasma in the peritubular capillaries through the cells of the proximal convolution of the tubule to its lumen; (3) tubular resorption, or the partial removal of solutes and water from the lumen of the distal half of the tubule by its cells (the corrective conservation of certain solids and of water wastefully excreted by the renal corpuscle).

The adequacy of these processes in the indispensable regulation of the composition of the plasma is dependent on the functional integrity of the glomeruli and tubules, as maintained normally by the free passage of blood through the complex glomeruli. Occlusion of the latter (fig. 12) or of their arterioles is followed by a breakdown of the vital heterogeneous equilibriums between tissue and fluids in the whole body.

This paper will present a discussion of the formation of urine under normal and under diuretic conditions and of the present knowledge of the chief factors involved. The data of the text and of the figures have been selected with care and in the hope that they are as reliable as is possible at the present time. The text was designed to be separate from the figures so that each might constitute an intelligible unit. The order of presentation is as follows: (1) the structural basis of the formation of urine in man and in other vertebrates; (2) the role of the blood plasma in the formation of urine; (3) glomerular filtration; (4) tubular excretion (secretion) and resorption; (5) diuretics; (6) diureses and renal oxygen consumption; (7) conclusions.

THE STRUCTURAL BASIS OF URINE FORMATION

The Renal Unit in Man.—There are approximately a million individual structures in the kidney, each composed of a glomerulus, or vascular unit, and a tubule (nephron), or epithelial unit (figs. 1 to 4). The vascular unit is significant because of the large surface afforded for the passage from the plasma of water and solutes by its forty to fifty

From the Department of Anatomy, School of Medicine, University of Buffalo.

nonanastomosing capillary loops, each about 9 microns in diameter and 0.5 mm. in length. Blood enters and leaves these capillaries through an afferent and an efferent arteriole, respectively. These arterioles are otherwise important because, owing to the smooth muscle of their walls

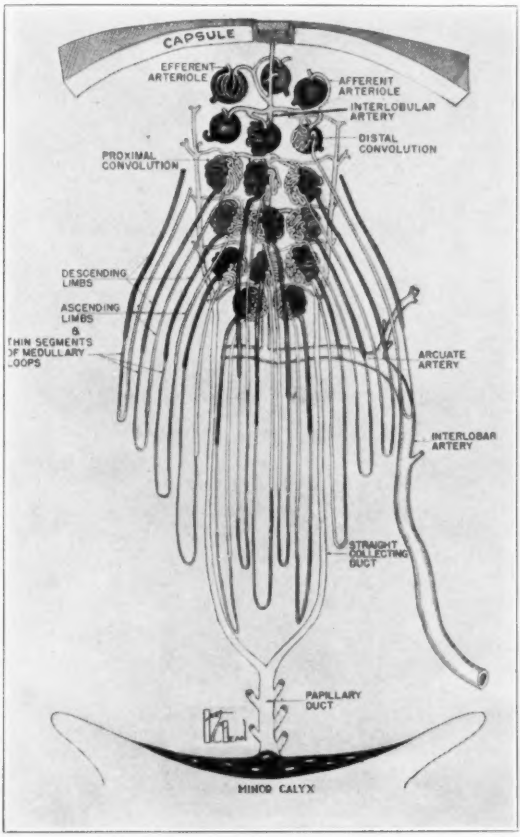

Fig. 1.—Interlobular renal architecture. (Modified and redrawn after Braus, H.: Anatomie des Menschen, Berlin, Julius Springer, 1924.)

and its innervation, they regulate functionally and with marked efficiency the glomerular capillary pressure (see also Goormaghtigh and Handovsky [1]). The lumens of both afferent and efferent arterioles near the glomerulus are, under uniform conditions, about 24 microns in diameter

1. Goormaghtigh, N., and Handovsky, H.: Effect of Vitamin D_3 (Calciferol) on the Dog, Arch. Path. **26**:1144-1182 (Dec.) 1938.

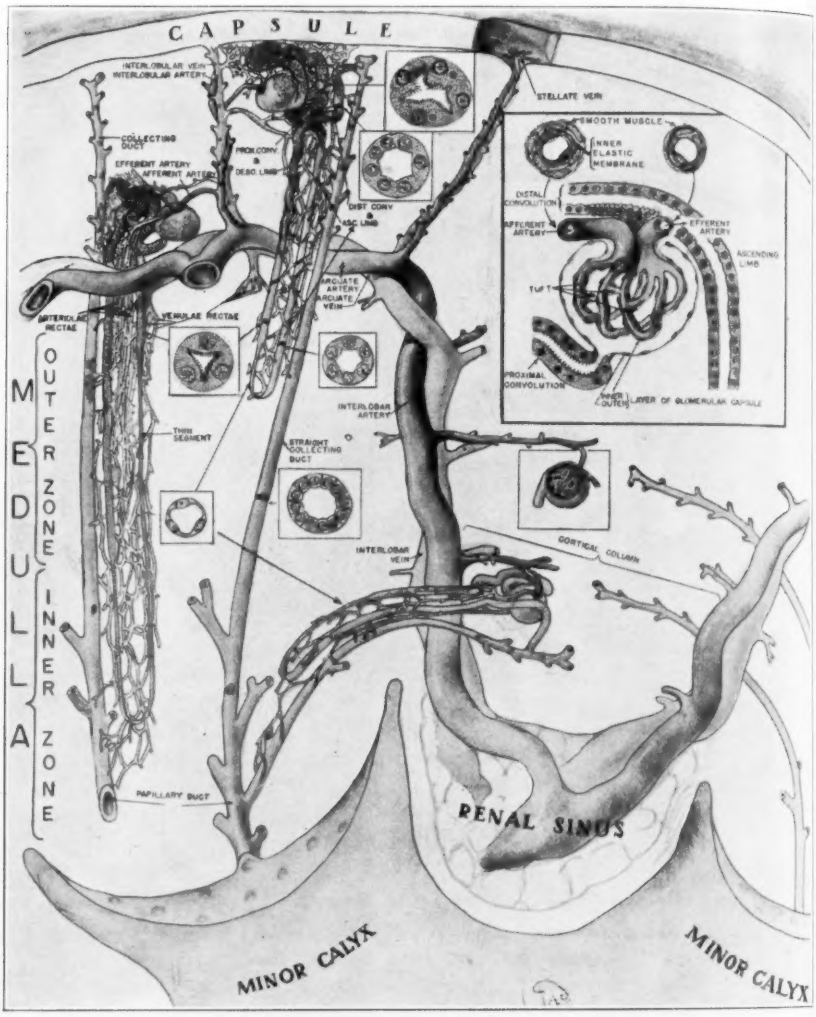

Fig. 2.—Structure of the human kidney. (By the author and self-explanatory, except that in the inset, between and above the afferent and the efferent arteriole, the location of a part of the afferent arteriolar cuff and the epithelial plaque, respectively, should be noted. These were first described by Goormaghtigh [Les segments neuro-myo-artériels juxta-glomérulaires du rein, Arch. de biol., Paris **43**:575-591, 1932].)

after fixation. Either may vary in size independently of the other as a result of one or more factors which may separately affect their walls or contents.

Fig. 3.—The architecture of the glomerulus. (Modified and redrawn after Vimtrup, B.: On the Number, Shape, Structure and Surface Area of the Glomeruli in the Kidneys of Man and Mammals, Am. J. Anat. **41**:123-151 [March] 1928.)

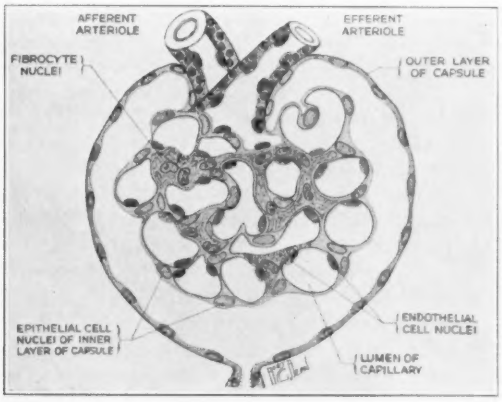

Fig. 4.—Section of a renal corpuscle. (By the author; self-explanatory.)

EXPLANATION OF FIGURE 5

The content and concentration relative to plasma of body fluids and the partitions between them; pressures in millimeters of mercury.

The sources of the data in the upper section are as follows:

Plasma-Lymph: Heim, J. W.: On the Chemical Composition of Lymph from Subcutaneous Vessels, Am. J. Physiol. **103**:553-558 (March) 1933.

Serum-Chest: Loeb, R. F.; Atchley, D. W., and Palmer, W. W.: On the Equilibrium Condition Between Blood and Serous Cavity Fluids, J. Gen. Physiol. **4**:591-595 (May) 1922.

Spinal Fluid: Fremont-Smith, F.; Dailey, M. E.; Merritt, H. H.; Carroll, M. P., and Thomas, G. W.: The Equilibrium Between Cerebrospinal Fluid and Blood Plasma, Arch. Neurol. & Psychiat. **25**:1271-1289 (June) 1931. Cockrill, J. R.: Nonelectrolytes: Their Distribution Between the Blood and the Cerebrospinal Fluid, ibid. **25**:1297-1306 (June) 1931.

Serum-Aqueous Humor: (Man) Walker, A. M.: Comparison of the Chemical Composition of Aqueous Humor, Cerebrospinal Fluid, Lymph, Inorganic Phosphate, Uric Acid, Urea, J. Biol. Chem. **101**:269-287 (June) 1933. *(Horse)* Duke-Elder, W. S.: XI. The Biochemistry of the Aqueous Humor, Biochem. J. **21**: 66-77, 1927.

Plasma-Glomerular: Walker, A. M., and Elsom, K. A.: A Quantitative Study of the Glomerular Elimination of Urea in Frogs, J. Biol. Chem. **91**:593-616 (May) 1931. Bordley, J., III; Richards, A. N.; Walker, A. M.; Reisinger, J. A.; Westfall, B. B., and Findley, T.: Quantitative Studies of the Composition of Glomerular Urine: VIII-XII, ibid. **101**:193-267 (June) 1933; **107**:661-672 (Dec.) 1934. Churchill, E. D.; Nakazawa, F., and Drinker, C. K.: The Circulation of Body Fluids in the Frog, J. Physiol. **63**:304-308 (Aug.) 1927.

Plasma-Sweat: McSwiney, B. A.: The Composition of the Human Perspiration, Proc. Roy. Soc. Med. **27**:839-848 (May) 1934.

The partitions, lowermost reading down and with stroma and capillary above each partition (first four), are as follows: lymphatic capillary endothelium; pleural lining; epithelium of choroid plexus; ciliary epithelium; epithelium surrounding a portion of a glomerular capillary, and a cross section of the secretory portion of a sweat gland.

The references for the pressures are as follows:

Capillary Blood (Man): Landis, E. M.: Capillary Pressure and Capillary Permeability, Physiol. Rev. **14**:404-481 (July) 1934.

Plasma-Colloid: Kylin, E.: Studien über den kolloidosmotischen Druck im Arterien und Venenblut, Arch. f. exper. Path. u. Pharmakol. **159**:401-407, 1931.

Capillary Blood and Colloid Osmotic Pressure (Frog): Landis, E. M.: Capillary Pressure and Capillary Permeability, Physiol. Rev. **14**:404-481 (July) 1934.

Glomerular Capillary Blood: Hayman, J. M., Jr.: Estimations of the Afferent Arteriole and Glomerular Capillary Pressures in the Frog Kidney, Am. J. Physiol. **79**:389-409 (Jan.) 1927.

Intraocular (Man): Adler, F. H.: Clinical Physiology of the Eye, New York, The Macmillan Company, 1933. The capillary blood pressures are approximations. The figures $30 + 25$ under plasma colloid osmotic pressure represent the colloid osmotic pressure of blood and the intraocular pressure in the anterior chamber of the eye.

PARTITIONS | CA | K | NACl | DEXTROSE | INORGANIC P | UREA | CREATININE | URIC ACID | AMINO ACID | NPN | PROTEIN | pH | SRG. | FLUID ANALYZED | ANIMAL

ANIMAL	FLUID ANALYZED	SRG.	pH	PROTEIN		NPN	AMINO ACID	URIC ACID	CREATININE	UREA	INORGANIC P	DEXTROSE	NACl	K	CA	PARTITIONS
				OS.PR.	%	MILLIGRAMS PER 100 CC										
DOG	PLASMA	1.028	7.4	30.0	6.18	32.6	4.90		1.37	21.7	5.6	123.0	678.0	20.0	11.7	
	LYMPH	1.015	7.6	12.3	3.32	34.8	4.84		1.40	23.5	5.9	132.0	711.0	18.4	9.84	
MAN	SERUM	1.023			5.0	38.0				120.0		124.0	646.0	13.0	9.6	
	CHEST	1.009			0.6	34.0				110.0		136.0	699.0	6.6	5.0	
MAN	SERUM	1.028	7.5		7.2	27.0		4.72	1.66	27.8	3.8	98.0	593.0	20.9	9.52	
	SPINAL FLUID	1.005	7.5		0.03	18.0		1.67	1.11	10.4	1.4	65.0	726.0	14.7	4.73	
MAN	SERUM		7.4					3.6		36.4	3.45	107.7				
	AQUEOUS HUMOR		7.6					2.8		12.9	1.92	59.7				
HORSE	SERUM				7.37	24.0	35.0		2.0	27.0	3.0	91.0	603.0	20.0	10.6	AS ABOVE
	AQUEOUS HUMOR				0.02	23.6	29.0		2.0	28.0	3.0	98.0	621.0	18.0	6.0	
FROG	PLASMA		7.7	5.26	2.0			4.04		18.6	3.65	66.0	505.0			
	GLOMERULAR		7.7		0.015			4.07		17.8	3.63	64.3	513.0			
MAN	PLASMA	1.028	7.4				6.0-N	2.81		26.0		100.0	600.0	19.9	10.2	
	SWEAT	1.003	6.14				5.0-N	1.56		45.9		12.6	370.0	19.5	11.3	

PRESSURES—MM HG

ANIMAL	CAPILLARY BLOOD	CAPILLARY BLOOD PRESSURE	PLASMA COLLOID OS.PR.	EFFECTIVE FILTRATION & ABSORBTION (-) PR.
MAN	ARTERIAL	34.6	26.6	8.0
	VENOUS	12.0	23.9	-11.9
FROG	ARTERIAL	10.8	7	3.8
	VENOUS	7.40		0.4
	GLOMERULAR	15.00		8.0
MAN	ARTERIAL INTRAOCULAR	57.00	30.0+25.0*	2.0
	VENOUS INTRAOCULAR	25.00	27.0	-2.0

Figure 5

Since, according to the prevailing conception, most of the renal blood must first pass through the glomeruli before reaching the peritubular capillaries, what occurs during such passage should be considered not as the initial or central aspect in the formation of urine but in relation to subsequent events. It is known, for example, that urinary water is derived from the plasma, chiefly while the latter is passing through the glomerular capillaries. The proteins of this dehydrated plasma normally do not pass in appreciable quantity through the walls of these capillaries. That which prevents their passage is the inner layer of an apical modification of the tubule called the glomerular capsule. (Glomerulus and capsule constitute a renal corpuscle.) This capsule is a two-layered structure, each layer of which is composed of flat epithelial cells. The inner layer, formed by proliferation in fetal life completely invests the glomerular capillaries. Capillary endothelium does not of itself normally prevent the passage of a certain amount of protein (note data for lymph and plasma, fig. 5). In the efferent arteriole and its initial peritubular capillaries the increased concentration of protein in the dehydrated plasma causes an increase in colloid osmotic pressure while the hydrostatic pressure is decreasing or minimal. This situation favors some resorption of the contents of that part of the tubule supplied by these capillaries but may be modified or made ineffective by the intervening cells and other factors.

Another question of interest concerns the existence of numerous renal arteriovenous anastomoses [2] and the possible effect on the formation of urine of the blood that may be shunted to the tubules without passing through the glomeruli. It is probable that glomerular capillary resistance to blood flow and, especially, the normal serial, temporary cessation of flow through about 25 per cent of the glomeruli [3] can so affect renal arterial pressure that arterial blood may pass into anastomotic veins, reverse the flow of incoming capillary blood and reach the peritubular capillaries. This would restore blood volume and raise the pressure in these capillaries, thereby favoring secretion. However, the spatial relations of the two most dynamic and phylogenetically oldest segments of the tubule, i. e., the proximal and distal convolutions (fig. 1), are such that it appears impossible to interpret their disparate function in terms of blood supply or pressure.

The portion of the tubule which leads from the capsule is structurally and functionally the most differentiated. Its correct designation is the proximal convolution with a descending limb. Its cells transport certain of the plasma's constituents directly to the lumen of this portion

2. Spanner, R.: Ueber Gefässkurzschlüsse in der Niere, Anat. Anz. (supp.) **85**:81-90, 1938.

3. Hayman, J. M., Jr., and Starr, I., Jr.: Experiments on the Glomerular Distribution of Blood in the Mammalian Kidney, J. Exper. Med. **42**:641-659 (Nov.) 1925.

and also are probably active in the synthesis of substances other than the ammonia and hippuric acid known to be formed in the kidney. The upper part of the descending limb leads abruptly into a straight, more deeply medullary portion of variable length, which, because of its small diameter, is called the thin segment. The thin segment attains its highest development in mammals. Its cells are flat, although not so flat as those of the capsule; the lumen, therefore, constitutes most of its diameter and

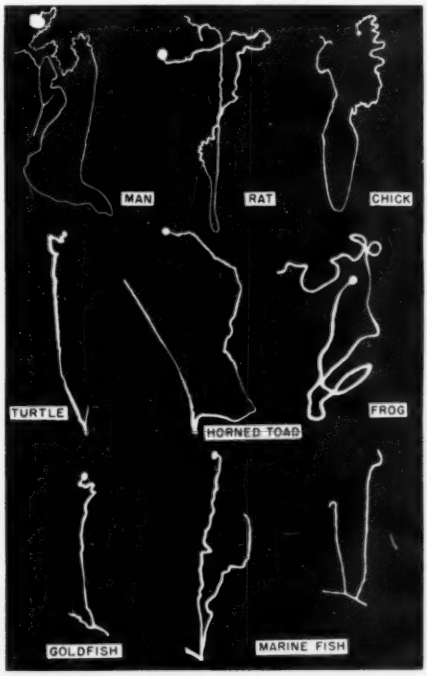

Fig. 6.—Photomicrographs of renal units isolated by the author. Note the two tubules constituting the lower center figure, the one long and glomerular and the other short and aglomerular. These two types are present in the same kidney and presumably are simultaneously functional. At the lower right are shown two aglomerular tubules from a kidney totally lacking glomeruli.

is about as large as that of the adjacent, thick portions. It is claimed that some of the water in the lumen of this segment passes through its cells to the peritubular blood.[4]

4. Gersh, I., and Stieglitz, E. J.: Histochemical Studies on the Mammalian Kidney: I. The Glomerular Elimination of Ferrocyanide in the Rabbit and Some Related Problems, Anat. Rec. **58**:349-367 (March 25) 1934.

The thin segment is also sharply demarcated from the ascending limb. This limb extends, parallel with the descending limb, from various levels in the medulla to its glomerulus in the cortex (fig. 1). Here it or the initial portion of the distal convolution is attached by an elliptic plaque of narrow columnar cells to the vascular pole of the corpuscle [5] and is succeeded by the coiled distal convolution proper. Its cells are primarily active in the resorption of water, while those of the distal convolution are similarly active in the resorption of solutes.[6] In the frog and the rat it is in the lumen of the middle third of the distal convolution that the p_H of the fluid, hitherto the same as that of plasma, drops as a result of the resorption of base, or its equivalent.[7]

In addition to the structurally different parts of the tubule, there is good evidence that in the proximal and distal convolutions there are several functionally discrete segments which have not been histologically recognized. In the kidneys of the cat and dog the presence of fatlike globules or vacuoles in certain cells of the proximal convolution and apparent changes in the contour of cell boundaries might properly be regarded as more indicative of functional than of structural specificity. Other indications of such specificity in this convolution are seen in human and other mammalian kidneys. For example, by the use of suitable methods iron is normally demonstrable in the cells of 2 to 3 mm. of the third quarter of the proximal convolution. After the introduction of large amounts of urea into the dog [8] or the rat (the only animals studied) the cells of 2 to 3 mm. of the second quarter of the convolution are definitely affected (fig. 9). Also, in chronic nephritis and

5. Goormaghtigh, N.: L'appareil neuro-myo-artérial juxta-glomérulaire du rein; ses réactions en pathologie et ses rapports avec le tube urinifière, Compt. rend. Soc. de biol. **124**:293-296, 1937.

6. (*a*) Okkels, H.: Différences entre les diverses cellules du troisième segment du tube urinaire chez les vertèbres, Bull. d'histol. appliq. à la physiol. **6**: 12-33 (Jan.) 1929. (*b*) Edwards, J. G.: Functional Sites and Morphological Differentiation in the Renal Tubule, Anat. Rec. **55**:343-367 (March 25) 1933. (*c*) Feyel, P.: Sur l'existence et le rôle de cellules spéciales dans le segment intermédiare et le tube de Bellini du rein chez la souris, Compt. rend. Soc. de biol. **115**:1148-1151, 1934. (*d*) Walker, A. M.; Hudson, C. L.; Findley, T., Jr., and Richards, A. N.: The Total Molecular Concentration and the Chloride Concentration of Fluid from Different Segments of the Renal Tubule of Amphibia, Am. J. Physiol. **118**:121-129 (Jan.) 1937.

7. (*a*) Montgomery, H., and Pierce, J. A.: The Site of the Acidification of the Urine Within the Renal Tubule in Amphibia, Am. J. Physiol. **118**:144-152 (Jan.) 1937. (*b*) Edwards, J. G.: Demonstrable Functions of the Renal Tubule After It Has Been Segmentally Injured by the Action of Mercuric Chloride, ibid. **119**:302 (June) 1937.

8. Hartman, F. W.: Methods and Effects of Increasing the Urinary Constituents in the Body, J. Exper. Med. **58**:649-662 (Dec.) 1933.

after mercurial poisoning marked changes (compensatory hypertrophy [9] and injury,[7b] respectively) occur in segments of this convolution, with which is associated a diminution of the renal phosphatase content.[10]

These structural and functional indications that each part of the tubule is in some specific way active in the formation of urine suggests two

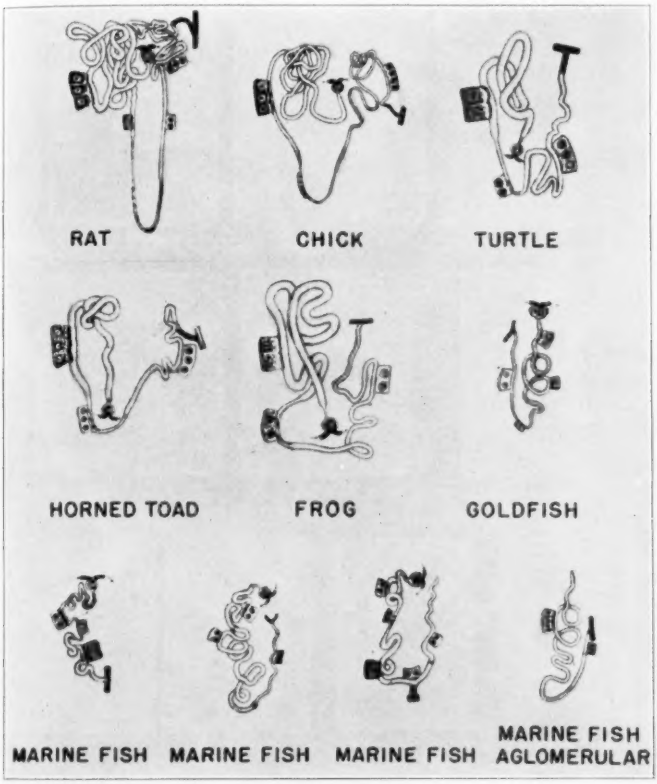

Fig. 7.—Diagrams of various renal units with insets which indicate something of the character of the epithelium of the units' component segments.

queries: 1. How do the cells of these parts in transporting water and solutes to and from the lumen of the tubule and peritubular capillaries

9. Oliver, J., and Luey, A. S.: The Morphology of the Abnormal Nephron in Terminal Hemorrhagic Bright's Disease, Arch. Path. **18**:777-816 (Dec.) 1934.

10. Brain, R. T., and Kay, H. D.: Kidney Phosphatase Enzyme in Disease, Biochem. J. **21**:1104-1108, 1927.

overcome osmotic or other resistance such as should, to some extent at least, exist between luminal, cellular, interstitial and capillary fluids? 2. How do cells in one portion of the distal convolution which are seemingly identical in structure with those in an adjacent portion constitute a segment so specific in its selection of substance to be resorbed that the p_H of the luminal fluid of this segment is changed?

The Renal Unit in Other Vertebrates.—Figures 6 and 7 show various renal units. The simplest unit is a coiled tubule which, throughout its length, is structurally similar to the proximal convolution in the kidney of all classes of vertebrates. This is the aglomerular tubule. The kidneys of certain fish contain tubules solely of this type and excrete urine whose constituents are like those of the urine of vertebrates in general (fig. 8).

	CERTAIN FISH *Non-or Aglomerular Mesonephros*		FROG *Glomerular Mesonephros*		TURTLE *Glomerular Metanephros*		BIRD *Glomerular Metanephros*		RAT *Glomerular Metanephros*		HUMAN *Glomerular Metanephros*	
CONSTITUENT	BLOOD	URINE	BLOOD	URINE	SERUM	URINE	PLASMA	URINE	PLASMA	URINE	PLASMA	URINE
Nonprotein N	52.0	197.0	13.13	78.4	66.0	400.0		100.0	45.0	773.5	31.0	1120.0
Urea	56.0	35.0	21.4	139.1	38.4	107.0		22.3	40.4	1258.3	30.0	2084.0
Uric Acid	0.84	1.7	0.7	0.12	0.5	40.4	6.0	197.0		13.3	2.0	60.0
Ammonia	6.8	44.7		4.6		43.2		21.0		96.9	1.0	59.5
Creatine	4.47	268.4	1.6	4.3	4.8	20.5	5.0	14.0		93.4	5.0	
Creatinine	1.49	42.6	2.3	2.9	1.7	9.2	1.3	4.0	0.6	48.4	1.5	107.7
Undetermined N			1.5	7.0	30.5	66.5		1.4		48.8	9.3	38.4
Sodium	556.0	188.0		11.1			265.0	94.0			300.0	350.0
Chloride	646.0	447.0	275.0	38.0	263.0	13.0	415.0	146.0	312.0	134.0	375.0	500.0
Potassium	25.0	10.0		7.5							20.0	137.0
Calcium	10.5	60.0		17.0	92.0	60.0		281.6			10.0	15.0
Magnesium	11.0	179.0		0.3							3.0	6.0
Phosphorus	25.2	5.4	5.3	6.9	6.6	51.6	4.0	36.0	6.7	64.6	3.0	150.0

Fig. 8.—Analysis of the blood and urine of vertebrates, expressed in milligrams per hundred cubic centimeters. The figures are original data of the author's except the analyses of the blood and urine of the fowl and man, for the acknowledgment of which see Edwards, J. G., and Condorelli, L.: Am. J. Physiol. **86**:383-398 (Sept.) 1928.

The glomerular renal unit is generally composed of (1) a corpuscle (fig. 4); (2) a neck segment, which in cold-blooded animals is short, narrow and usually ciliated but in warm-blooded animals is merely a sharp transition from the squamous epithelium of the corpuscle to the columnar epithelium of the next segment; (3) a proximal convolution, composed of acid-staining, brush-bordered cells, which constitutes the longest subdivision of the tubule; (4) in cold-blooded animals an intermediate segment, which is usually interposed between the proximal and the distal convolution and which averages 0.2 mm. in length, or, in warm-blooded animals, a thin segment, 1 to 10 mm. long, which occupies

a similar locus in the tubule; (5) a succeeding distal convolution, composed of light-staining, more or less cuboidal cells (in the mammalian and to some extent in the avian kidney it is preceded by an ascending limb composed of similar cells).

The renal tubule of marine fish differs in one major respect from that of fresh water fish and other vertebrates: it lacks a distal convolution.

Fig. 9.—The segmental effect on the proximal convolution (light-staining portions) of the tubule in the rat's kidney following repeated intraperitoneal injections of 5 cc. of a 20 per cent solution of urea.

However, the urine of these fish and that of other vertebrates are comparable (fig. 8). In marine and in fresh water fish the tubules, or proximal convolutions, are multisegmental and bisegmental, respectively, regardless of the relatively insignificant glomerular development in marine fish. The glomerular tubule is structurally more differentiated and is of greater length than the aglomerular tubule.

The *proximal* convolution is the only part of the renal unit that is invariably present in the kidney of all classes of vertebrates. This fact, and others pertaining to the tubule in general, seem to warrant inclusion of the data [11] given in the following tabulation and in the succeeding paragraphs and tabulations.

Subject and Age	Renal Mass, Cc.	Number Glomeruli per Given Renal Mass	Diameter, Microns	
			Glomeruli	Proximal Convolution
Premature birth	6.5	122	85	..
Girl, 1	21.0	46	88	38
Girl, 4	55.0	18	150	53
Girl, 5	60.0	17	149	51
Girl, 18	115.0	11	190	54
Man, 32	120.0	10	213	55
Man, 40	130.0	11	195	53
Woman, 46	120.0	9	196	65

The number of glomeruli per cubic millimeter of renal cortex in man and the pig is 4 to 6; in the rat and the guinea pig, 15; in the crow, 90 to 100; in the duck, 230 to 300; in the weaver bird, 400 to 450. These data indicate the relative space occupied by glomeruli and tubules in mammals and birds.

Measurements of various renal units are given in the following tabulation in order to show, comparatively, the diameter in microns of the glomerulus, G, or vascular unit; the length in millimeters of the proximal convolution, PC, or secretory unit; the length of the thin segment, TS, ascending limb, AL, and distal convolution, DC, which collectively are to be regarded as the resorptive unit. The total length of the tubule, TL, is also given.

	G	PC	TS	AL	DC	TS+AL	AL+DC	TS+AL +DC	TL
Man	200	14	6	9	4.6	15.0	13.6	19.6	38.6
Ox	190	19	12	10	1.3	22.0	11.3	23.3	42.3
Pig	240	19	5	5	2.5	10.0	7.5	12.5	31.5
Sheep	180	16	8	7	2.0	15.0	9.0	17.0	33.0
Rabbit	110	7	6	4.5	0.8	10.5	5.3	11.3	18.3
Cat	124	9	8	6	1.2	14.0	7.2	15.2	24.2
Rat	100	11	5	8	1.5	13.0	9.5	14.5	25.5
Mouse	80	3	2	1.5	0.7	3.5	2.2	4.2	7.2
Porpoise	130	5	4	2.5	1.3	6.5	3.8	7.8	12.8
Chick	40	6	1.5	3.5	4.0	5.0	7.5	9.0	14.0
Turtle	50	2	0.2	..	1.4	....	....	1.6	3.6
Frog	100	3.8	0.2	..	3.0	....	....	3.2	7.0
Goldfish	60	2	0.2	..	1.5	....	....	1.7	3.7
Marine fish									
Glom	30-90	5	..	..	...	....	....	....	5.0
Aglom	...	3	..	..	...	....	....	....	3.0

Because, in general, in all classes of vertebrates, solutes and some water are transported from peritubular capillaries to the lumen of the proximal convolution, and (except in marine fish) water and solutes are transported from the lumen to peritubular fluid or capillary blood in the remainder of the tubule, the tubule is divisible functionally into a mini-

11. von Möllendorff, W.: Handbuch der mikroscopischen Anatomie des Menschen, Berlin, Julius Springer, 1930, vol. 7, pt. 1, pp. 1-374.

mum of two segments: namely, a proximal convolution or secretory unit and a distal convolution or resorptive unit. In the foregoing data the lengths of these two segments are given in black letter type (PC, the length of the proximal convolution, and TS + AL + DC, the sum of the lengths of the remaining portions of the tubule). It is noteworthy that the length of the proximal convolution in mammals and in the chick is less than the sum of the lengths of the remaining portions, while the

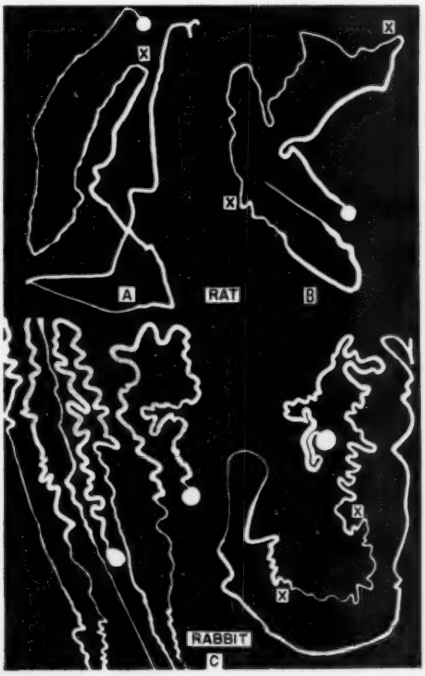

Fig. 10.—Photomicrographs of renal units isolated by the author showing the extent and segmental character of the lesions in the proximal convolution induced by mercury under various conditions. In *A*, from the glomerulus (knob) at top to *X*; in *B* and *C*, right, *X* to *X*, and in *C*, left, narrow portions except for the thin segment (normal) in the lower part of the third tubule from the left.

opposite is true in cold-blooded animals. The different lengths of the resorptive portions probably constitute the basis for the fact that mammalian urine is normally hypertonic; that of the chick, hypertonic or isotonic, and that of the cold-blooded animals, definitely hypotonic.[12]

12. Edwards, J. G., and Condorelli, L.: Studies on Aglomerular and Glomerular Kidneys: II. Physiological, Am. J. Physiol. **86**:383-398 (Sept.) 1928.

BLOOD PLASMA AND URINE FORMATION

Blood plasma is the immediate source of body fluids. Their composition relative to plasma (fig. 5) indicates that some are filtrates. Filtrates are colloid free but are otherwise identical in composition with the

Fig. 11.—Photomicrographs of a rabbit's kidney. *A* shows well preserved upper portions of proximal convolutions and two renal corpuscles whose outlet to the tubule has become occluded by connective tissue within three months after the injection of 10 mg. of mercury. In *B* is shown the character of the lesion observable in 2 mm. of the lower third of the proximal convolution in the kidney of the same animal.

plasma, from which they are derived as the result of an excess of hydrostatic over colloid osmotic pressure in the blood capillaries. That fluids derived from plasma may differ significantly from it in composition or in concentration is attributable to the character of the epithelial partitions

Fig. 12.—Diagrams of various stages in glomerular degeneration. In *A*, *B* and *C* is indicated the decrease in number of glomeruli (solid black) occurring in chronic arteriosclerotic nephritis. In *D*, top, left, is shown a preglomerular branch of an efferent arteriole, a looped shunt remaining after occlusion of the other glomerular capillaries, and the efferent arteriole with bifurcated termination. In *D*, top, right, is shown a two-looped shunt between afferent (right) and efferent arterioles. The two middle diagrams in D represent a continuation of afferent and efferent arterioles, with marked atrophy of the slightly attached glomeruli. The two lower diagrams illustrate, left, an earlier stage in the glomerular atrophy; right, a normal glomerulus. In *E*, *F* and *G* are shown stages in the development of glomerular, intercapillary connective tissue resulting in occlusion of the capillaries and atrophy of the glomerulus. (*A*, *B* and *C*, after Loomis, D.: Plastic Studies in Abnormal Renal Architecture: IV. Vascular and Parenchymal Changes in Arteriosclerotic Bright's Disease, Arch. Path. **22:** 435-463 [Oct.] 1936. *D*, six schematic diagrams by the author, based on the cited work of Loomis. *E* and *F*, after Bell, E. T.: A Text-Book of Pathology, ed. 3, Philadelphia, Lea & Febiger, 1928. *G*, after MacCallum, W. G.: A Text-Book of Pathology, ed. 6, Philadelphia, W. B. Saunders Company, 1936.)

through which they pass.[13] Squamous cells are present at the site of the formation of approximate filtrates (in fig. 5, under "Partitions," note the lymphatic endothelium and the epithelial investment of a glomerular capillary). Also, in the development of the mammalian kidney, the epithelium of the inner layer of the glomerular capsule does not appear to function until it has become adequately squamous.[14]

Several factors suggest that the fluid in the glomerular capsule is a filtrate. For example, when the intracapsular pressure equals the effective filtration pressure (glomerular capillary pressure in excess of colloid osmotic pressure) formation of an appreciable amount of intracapsular fluid generally stops; likewise, such formation ceases when the hydrostatic capillary pressure equals the plasma colloid osmotic pressure. The fluid in the glomerular capsule of cold-blooded animals is approximately a plasma filtrate. Data on the frog are given in table 1. Independent confirmation of the analysis of this filtrate is unfortunately lacking. There is, nevertheless, considerable evidence that filtration is responsible for the presence of the intracapsular fluid and, as such, constitutes an important aspect of urine formation. However, this fluid should not be referred to as glomerular or provisional urine because a plasma filtrate is not urine. Urine formation begins, continues and ends in the tubule, regardless of whether urinary constituents are immediately derived from intracapsular or from peritubular fluid. The processes involved in urine formation are commonly designated as filtration, secretion and resorption, but the formation of a plasma filtrate has nothing to do with its subsequent differentiation.

Recent studies of the kidneys of mammalian fetuses and of developing chicks show that the cells of the proximal convolution become functional before those of the glomerular capsule.[14] Just what functional changes may be initiated in the cells of this convolution or in the tubule as a whole, after the requisite flattening of the inner layer of the capsule and the coincident formation of intracapsular fluid, are at present entirely speculative. I [15] have called attention to structural and probable functional changes in the tubule contingent on its attachment to a glomerulus.

I conceive of urine formation as proceeding simultaneously in the several parts of the tubule, accompanied by the formation of an intracapsular filtrate. During the passage of the latter through the tubule,

13. Flexner, L. B., and Stiehler, R. D.: Biochemical Changes Associated with the Onset of Secretion in the Fetal Chorioid Plexus: An Organization of Oxidation-Reduction Processes, J. Biol. Chem. **126**:619-626 (Dec.) 1938.

14. Gersh, I.: The Correlation of Structure and Function in the Developing Mesonephros and Metanephros, Publication 479, Carnegie Institution of Washington, 1937; Contrib. Embryol. (no. 153) **26**:33-58 (Jan.) 1937.

15. Edwards, J. G.: The Epithelium of the Renal Tubule in Bony Fish, Anat. Rec. **63**:263-279 (Oct. 25) 1935.

some of it is resorbed and the remainder becomes urine. (Other filtrates, comparable except for their content of protein or a difference in the concentration of their constituents relative to plasma, become such fluids as interstitial fluid or lymph, aqueous humor, cerebrospinal fluid and endolymph.) Fractions of the filtrable plasma pass simultaneously into the lumen of the tubule via the corpuscle and the cells of the proximal convolution, to be returned in part to peritubular fluid or capillary blood by the cells of the remaining portions of the tubule. There is no valid proof as yet that any constituent normally present in the urine arrives there from the plasma solely by passage through the renal corpuscle.

It is interesting that in the frog the dextrose which enters the tubule from the glomerular capsule gradually disappears during its passage through the lumen of the proximal convolution, while at the same time and in the same area the concentration of urea increases.[16] In other vertebrates (fish, an amphibian, the chick, anthropoid ape and man) it is presumed that dextrose disappears as the creatinine increases [17] (comparably with urea in the frog). It is demonstrable that in the kidneys of diabetic persons glycogen is deposited in the cells of a segment of the proximal convolution. When the cells of the latter are poisoned by the glucoside phlorhizin, dextrose is copiously excreted, but there is little or no change in the quantitative excretion of other urinary constituents. A somewhat similar situation obtains when a portion of this convolution is affected by mercury. Despite evidence that dextrose is resorbed by the cells of the proximal convolution, the possibility still remains that, instead of a direct transfer of this substance to peritubular capillaries, something quite different occurs.

All of the more pertinent and reliable data indicate that the concentration of the fluid in the lumen of the proximal convolution progressively increases as a result of the addition of solutes and possibly of the resorption of a small amount of water. This progressive concentration continues more rapidly in the next two segments of the tubule as a result of the resorption of a relatively large amount of water. In the distal convolution, solutes are resorbed.[18] The speed of resorption by the cells of a segment of this convolution in the frog's kidney has been shown by perfusing a single tubule with a 0.33 molar solution of sodium phosphate (p_H 7.5). The p_H of the luminal fluid shifted from 7.5 to 6.8 in one minute.[7a] It seems probable that the fluid in the lumen of the tubule is

16. Walker, A. M., and Hudson, C. L.: The Reabsorption of Glucose from the Renal Tubule in Amphibia and the Action of Phlorhizin upon It, Am. J. Physiol. **118**:130-143 (Jan.) 1937.

17. Smith, H. W.: The Physiology of the Kidney, New York, Oxford University Press, 1937, pp. 1-310.

18. Gersh and Stieglitz.[4] Walker and others.[6d] Edwards.[7b] Gersh.[14]

never in osmotic equilibrium with plasma, although it may be in such equilibrium with peritubular fluid. Therefore, the additions to this fluid and subtractions from it are made against osmotic gradients.

GLOMERULAR FILTRATION

Commendable efforts have been made during the past few years to measure glomerular filtration, despite the failure of Rehberg and others in this connection. A substance has been sought [19] which, without disturbing normal processes, would be excreted solely by filtration, without subsequent resorption. Some investigators are now convinced that the polysaccharide inulin is such a substance. If so, therefore, a reliable method is available for measuring glomerular filtration, for determining whether a given urinary constitutent is excreted by filtration alone or by filtration and tubular excretion and for estimating the degree of resorption of the constituent and of water. If a substance is filtered—that is, excreted—entirely via the corpuscle, the degree of its concentration in the urine will show the amount of water resorbed. The amount of inulin excreted in the urine in one minute (rate of excretion) divided by the amount contained in 1 cc. of plasma gives the volume of glomerular filtrate in cubic centimeters per minute (rate of filtration). When two or more substances, under a variety of conditions, are simultaneously excreted at rates identical in relation to their respective concentrations in the plasma it is claimed that such substances are excreted solely by filtration, without resorption. Further, if the plasma concentration of a substance which is eliminated in part by the cells of the tubule (creatinine is said to be such a substance) is raised variably above its normal level, the amount eliminated can be reduced until it approaches that supplied by glomerular filtration alone.

Without stating the details of the results obtained by several investigators in studies of the mode of excretion of certain foreign and normal substances, the possibilities inherent in such excretion may be summarized as follows.

1. If a substance is excreted by filtration but is partially resorbed, the rate of its excretion will be *less* than the rate of filtration.

2. If a substance is excreted by filtration and by the tubule but is not resorbed, the rate of its excretion will be *greater* than the rate of filtration.

3. When a substance is excreted by filtration and by the tubule, if an amount is then resorbed equal to the amount excreted by filtration or by the tubule, the rate of excretion will be equal to the rate of tubular excretion or of glomerular filtration, respectively.

19. Jolliffe, N.; Shannon, J. A., and Smith, H. W.: The Excretion of Urine in the Dog: III. The Use of Non-Metabolized Sugars in the Measurement of the Glomerular Filtrate, Am. J. Physiol. **100**:301-312 (April) 1932.

4. A substance may be excreted partly by filtration and partly by tubular excretion and may then be partially resorbed in such amounts that the rate of excretion is invariably less than the rate of glomerular filtration.

Whatever may be the mode of excretion of inulin, I am of the opinion that the precise mode of excretion of any normal urinary constituent has not been determined by the use of this substance.

TUBULAR EXCRETION

This discussion of tubular excretion is based on data compiled by Smith.[17] Just as inulin, a substance foreign to blood plasma, appears to be excreted by filtration alone, so another substance, phenolsulfonphthalein (phenol red), also foreign to the plasma, appears to be almost if not as completely excreted by the proximal convolution of the tubule, without being resorbed. Of the amount of phenolsulfonphthalein administered 94 per cent is excreted by the tubule. Since I have found that some of the dye is destroyed in the body or eliminated in the feces, the foregoing percentage may represent its total excretion in the urine. The rate of its excretion when the plasma contains 0.1 to 1.0 mg. per hundred cubic centimeters is much greater than that of inulin, although at such concentrations 80 per cent of the dye is bound to the albumin fraction of the plasma proteins. The rate of excretion is independent of the rate of urine formation and does not increase in direct proportion to the concentration of phenolsulfonphthalein in the plasma. Instead, as the concentration of phenolsulfonphthalein in the plasma is increased from 1 to 20 mg. or more per hundred cubic centimeters its excretion by the tubule is progressively decreased and, despite the increase in the amount of free dye at higher concentrations, the total excretion is reduced. Such behavior is said to be characteristic of substances excreted by the tubule, regardless of their filtrability, but not of those excreted by the corpuscle. Verne[20] noted similar excretory activity in the aglomerular kidney.

Several organic compounds of iodine are also excreted by the tubule with remarkable efficiency.[21] With regard to one of them (diodrast) it is said[22] that its excretion measures the effective renal blood flow (the volume of blood supplied to the secretory portion of the tubule), since this excretion is limited normally by blood flow but not, within a wide

20. Verne, J.: Contribution à l'étude des reins aglomérulaires; l'appareil renal des poissons lophobranches, Arch. d'anat. micr. **18**:357-407, 1922.

21. Landis, E. M.; Elsom, K. A.; Bott, P. A., and Shiels, E. H.: Simultaneous Plasma Clearances of Creatinine and Certain Organic Compounds of Iodine in Relation to Human Kidney Function, J. Clin. Investigation **15**:397-410 (July) 1936.

22. Shannon, J. A.: Renal Tubular Excretion, Physiol. Rev. **19**:63-93 (Jan.) 1939.

range, by the amount of the substance in the blood or by the excretory capacity of the tubule. Excretion of phenolsulfonphthalein, however, is limited by the amount of secretory tissue but is not correlated with blood flow or the concentration of the dye in the plasma.

Thus it follows, and is of clinical interest, that the excretion of inulin may be used as a measure of glomerular filtration; that of diodrast may be used as a measure (*a*) of renal blood flow and (*b*) (in conjunction with phenolsulfonphthalein or dextrose) of the amount of renal secretory tissue and of the functional state (normal or damaged) of the proximal convolution. However, such use of diodrast is still more a hope than a realization.

The preferred excretion of certain substances (inulin, sodium ferrocyanide) by the corpuscle and of others (iodine compounds) by the cells of the proximal convolution when all of them are completely filtrable—that is, they are not bound to plasma protein or of such molecular size as to limit their passage through the corpuscle—shows that filtrability cannot be a factor in their respective modes of excretion. That the excretion of iodine compounds by the cells of the proximal convolution is more efficient than that of inulin by the corpuscle is evidence of the excretory potency of this part of the tubule. This potency, together with the comparatively great size and length of the convolution in mammals and other vertebrates, especially in compensatory hypertrophy, should cause reluctance to accept such evidence as now seems to indicate, or is interpreted to indicate, that most urinary constituents are excreted by the corpuscle. The excretion of inulin may measure glomerular filtration, but, despite coincidences suggestive of a similar mode of excretion of other substances, it does not follow as yet that inulin can be reliably used to indicate the mode of excretion of normal urinary constituents.

Phylogenetically and actually, the tubule is responsible for the character of urine; but this does not mean that selective and partial resorption of a glomerular filtrate is the chief task which the tubule is normally required to perform, or that the initial and central feature in urine formation is glomerular filtration. For, while the urine in extreme diuresis approaches a plasma filtrate in the concentration of its constituents, a diuretic type of urine is excreted also by kidneys lacking glomeruli and distal convolutions.[23] There is no reason to give precedence to glomerular filtration over the other processes of urine formation. All three processes in the adult kidney are simultaneous and mutually interrelated, although developmentally the tubule is excretory before the corpuscle. In the urine-forming activity of the tubule, in both the aglomerular and the glomerular kidney, blood pressure is an incidental factor. In the

23. Bieter, R. N.: Further Studies Concerning the Action of Diuretics upon the Aglomerular Kidney, J. Pharmacol. & Exper. Therap. **49**:250-256 (Oct.) 1933.

filtrate-forming activity of the corpuscle, however, blood pressure is the major factor. These circumstances and others should be considered in the study of the total complex of the formation of urine.

DIURETICS

Substances inducing an increase in urine volume are definable as diuretics. Their use thus far has not revealed new factors in urine formation or renal function but has variably illustrated all the known factors. Abnormal increase or change in the percentage composition of the constituents of blood plasma is usually followed by a diuresis in which solutes are reduced in percentage but may be increased in total amount. Such diureses restore or tend to restore the normal composition, p_H, volume or osmotic pressure of plasma. This emphasizes the nature of normal as well as of heightened renal function and is reflected in the composition or in the volume of the urine.

The cations of the fixed bases, sodium and potassium, are excreted with considerable water when present in excess in plasma. Sodium, the predominant base in extracellular fluid, and potassium, that in intracellular fluid, are excreted (or retained) after changes affecting these fluids. These ions seem functionally different in general metabolism and in their action on the cells of the renal tubule. One indication of this difference is seen in adrenal insufficiency, in which excretion of sodium chloride and water is increased, while in the plasma potassium is increased and sodium chloride decreased. The relative immobility of potassium and its unfavorable effect on the sodium balance appear to constitute the basis for the behavior of the two ions under normal conditions and under those of diuresis and edema.

The ingestion or injection of the chlorides of ammonium, calcium and magnesium causes an increase of chloride in the plasma, a reduction of bicarbonate and a lowering of p_H and osmotic pressure. The attendant diuresis is marked by the excretion of water and fixed base and/or ammonia of renal origin.

Dextrose, urea and sodium chloride act as diuretics because, in addition to their effects on the plasma, their increased excretion limits the resorption of water from the lumen of the tubule. Such diureses are called "tubule" or osmotic diureses, in contradistinction to the "dilution" diureses attributable to excessive filtration without compensatory resorption. All diureses are the result of some antecedent changes which may affect singly or in combination the blood plasma and the cardiovascular, renal vascular and tubular systems. Salts, dextrose and urea are examples of "tubule" diuretics. It is probable that most diureses are, in considerable part, the result of increased filtration, which causes more of fluid to pass through the tubule than can be resorbed, or of the osmotic resistance to water resorption caused by the increased excretion of solutes. The

methyl purines, such as caffeine, seem to affect all of the systems mentioned, and therefore the urine may show the variable effects of changes in these systems.

Mercurials, mercupurin and acidifying salts cause (*a*) changes in the blood plasma, which bring about marked increase in the excretion of chloride; (*b*) changes in the glomeruli, which result in an increased filtration not necessarily related to changes in the plasma, and (*c*) changes in the cells of the proximal convolution. The diuresis is the product of increased filtration, secretion and osmotic resistance to water resorption (the last is perhaps a result of the presence of excess chloride in the lumen of the distal half of the tubule). With reference to mercury, this statement is not invalidated by obviously inconclusive reports of (*a*) evidence against an increased rate of filtration in salyrgan diuresis; (*b*) the action of mercury on the isolated kidney and (*c*) the results of its injection into the renal artery of an anesthetized dog. Increased volume and rate of flow of fluid through the lumen readily cause the resorptive capacity of the tubule to be exceeded. When substances are excreted in amounts which impede their own resorption and that of water, there is small need for further conjecture regarding the cause of the diuresis. Mercury does not affect appreciably the resorptive capacity of the tubule. Its action is limited chiefly to the proximal convolution, which has a minimal resorptive capacity. The glycuretic diuresis which often results from the action of mercury is caused by the presence of abnormal amounts of dextrose and chloride in the lumen of that part of the tubule distal to the proximal convolution. I have some evidence, however, that mercury can so affect this convolution that water and solutes pass as readily through its cells as through those of the corpuscle. If so, a diuresis could occur owing to the increased volume of flow through the tubule, in excess of its resorptive capacity. That the known capacity of the distal half of the tubule to resorb water, chloride, bicarbonate and possibly urea is but little, if at all, affected by the action of mercury is shown by appropriate decrease in the volume or rate of flow through the tubule; by the work done in resorption during diuresis, and by the results from injections of the antidiuretic hormone.

DIURESES AND RENAL OXYGEN CONSUMPTION

Available data indicate that the kidney has a high metabolism; in some forms of diuresis it may consume as much as 10 per cent of the oxygen consumed by the whole body. This is not surprising in view of the work done by the cells of the tubule in secretion, synthesis and resorption. In secretion, work is needed for the transfer of solutes from solutions presumably of higher to those of lower osmotic pressure while, at the same time and site, dextrose and perhaps phosphate pass through the lumen in the opposite direction. It is improbable that any effective

filtration pressure obtains in the peritubular capillaries (except possibly for a short distance from the efferent arteriole) unless it is transmitted to them through arteriovenous anastomoses. Therefore, resorption, without work, could occur at least from the lumen of the middle third of the tubule (the thin segment and the lower part of the ascending limb). But soon the luminal fluid, because of the resorption of water, has a higher osmotic pressure than does the plasma, whose osmotic pressure decreases in consequence of this same resorption. Accordingly, work must be done to transfer the solutes in the lumen from a higher to a lower osmotic pressure.

It is noteworthy that when diuresis occurs after intravenous injections of urea, sodium sulfate or phlorhizin there is said to be a marked increase in renal oxygen consumption. Often, however, it does not occur when diuresis follows injections of Ringer's solution or of sodium chloride. Renal oxygen consumption increases in proportion to blood flow but not to urine flow.[24] Increase in the rate of urea excretion is attended by an increase in blood flow, but, according to one investigator,[24] there is no increase in oxygen consumption. The percentage of urea in the urine is also greatly reduced after injections of Ringer's solution while that of sodium chloride or of sodium sulfate is not. During the diuresis of excessive filtration, contingent on a reduction of plasma proteins, the renal oxygen consumption is not increased. In other words, there is no increase in work done by the tubule. But when the proximal convolution is impaired by phlorhizin the accompanying diuresis involves a significant increase in oxygen consumption, although dextrose is presumably not resorbed by parts of the tubule other than this convolution, which under the action of phlorhizin cannot resorb it. This seems paradoxic, since phlorhizin appears not to affect the excretion and relative resorption of other urinary constituents. But account should be taken of the possibility that periods of heightened secretory activity in one part of the tubule may not coincide with similar periods of resorptive activity in another part; also, oxygen consumption by the cells of the proximal convolution may be reduced while that by the cells of the remainder of the tubule is not. Therefore, an increase in oxygen consumption by one part of the tubule may approximate or be identical with a decrease in another part, without significant change in the total amount of oxygen consumed. Since the glomerulus functions at the expense of the pumping heart while oxygen for the tubule is locally obtained, diuretics may not reveal consistent changes in renal oxygen consumption because of the important part played by the highly variable glomerulus in most diureses and because the limits of tubular activity are relatively fixed.

24. Van Slyke, D. D.; Rhoads, C. P.; Miller, A., and Alving, A. S.: Relationships Between Urea Excretion, Renal Blood Flow, Renal Oxygen Consumption, and Diuresis: The Mechanism of Urea Excretion, Am. J. Physiol. **109**:336-374 (Aug.) 1934.

CONCLUSION

1. In the kidneys of all classes of vertebrates the proximal convolution is primarily secretory and is the only part of the tubule invariably present. The structure and functions of the tubule, when viewed phylogenetically and when studied in health and in disease, would seem to have an importance much greater than is at present demonstrable in detail. Comparative renal studies dealing with the aglomerular kidney, and inaugurated by me in this connection, have been productive of much interest in secretion by the tubule. It is hoped that eventually the actual role of the tubule in urine formation will be established.

2. The phylogenic development of the corpuscle as the site of filtration is related to that of the distal convolution as the site of resorption. Filtrable substances in the plasma are excreted by the corpuscle regardless of possible depletion of body fluids and consequent damage to the tissues. The distal convolution, aided in birds and mammals by the thin segment and the ascending limb of the medullary loop, performs by resorption the function of salvage. The hypotonic urine of cold-blooded animals indicates that there has been resorption of relatively more of certian solutes than of water; the hypertonic urine of warm-blooded animals indicates the opposite.

3. A filtrable fraction of plasma is excreted into the lumen of the tubule by the corpuscle and by the cells of the proximal convolution. Minimal amounts of protein are present in this fraction because the passage of larger amounts is prevented by the epithelial wall adjacent to the glomerular and peritubular capillaries. Many factors so affect filtration by the corpuscle, however, that albuminuria readily develops. The extreme sensitiveness of this structure to such normal or pathologic changes as those which occur in the chemical composition of plasma or in blood pressure, flow or volume is responsible for confusing variations and dubious interpretations of its activity.

4. Diuretics are initially and chiefly effective by their direct or indirect action on one or more of the components of the cardiovascular system. Neither diuretic urine nor the subnormally concentrated urines formed after renal injury should be regarded as necessarily indicating impairment of the resorptive power of the tubule. Urines of low specific gravity may be variously formed as a result of excessive filtration, of decreased resorption of water or of increased resorption of solutes.

5. It is not yet established that the formation of urine is primarily the result of filtration and resorption or that resorption is the chief function of the tubule as a whole.

EFFECT OF SULFANILAMIDE AND SULFAPYRIDINE ON HEMOGLOBIN METABOLISM AND HEPATIC FUNCTION

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MINNEAPOLIS

Since sulfanilamide has come into general use, a number of reports have appeared indicating that jaundice [1] and hemolytic anemia [2] are toxic effects that may be encountered. One gains the impression from the majority of these reports that such complications are rarely encountered and that they are probably due to drug idiosyncrasy. Long and his associates [1g] observed but 2 patients with jaundice (without hemolytic anemia) among 408 treated with sulfanilamide. In the material from the same clinic, Wood [2b] noted that acute anemia developed in 21 of 522 persons to whom the drug was administered. He found the incidence of anemia to be 8.3 per cent in children as compared with 2.4

From the Division of Internal Medicine, University of Minnesota Hospital.

Aided by a grant from the research fund of the Graduate School, University of Minnesota.

Assistance in the preparation of materials was furnished by the personnel of Works Progress Administration Official Project No. 665-71-3-69.

1. (*a*) Hageman, P. O., and Blake, F. G.: A Specific Febrile Reaction to Sulfanilamide: Drug Fever, J. A. M. A. **109**:642 (Aug. 28) 1937. (*b*) Saphirstein, H.: Hepatitis and Toxic Erythema with Desquamation Due to Sulfanilamide, Urol. & Cutan. Rev. **42**:101, 1937. (*c*) Bannick, E. G.; Brown, A. E., and Foster, F. P.: Therapeutic Effectiveness and Toxicity of Sulfanilamide and Several Related Compounds, J. A. M. A. **111**:770 (Aug. 27) 1938. (*d*) Lockwood, J. S.; Coburn, A. F., and Stokinger, H. E.: Mechanism of Action of Sulfanilamide, ibid. **111**:2259 (Dec. 17) 1938. (*e*) Garvin, C. F.: Toxic Hepatitis Due to Sulfanilamide, ibid. **111**:2283 (Dec. 17) 1938. (*f*) Cline, E. W.: Acute Yellow Atrophy of the Liver Following Sulfanilamide Medication, ibid. **111**:2384 (Dec. 24) 1938. (*g*) Long, P. H.; Bliss, E. A., and Feinstone, W. H.: Mode of Action, Clinical Use and Toxic Manifestations of Sulfanilamide, ibid. **112**:115 (Jan. 14) 1939. (*h*) Watson, C. J.: The Effect of Sulfanilamide upon the Liver, Surgery **5**:616, 1939.

2. (*a*) Harvey, A. M., and Janeway, C. A.: The Development of Acute Hemolytic Anemia During the Administration of Sulfanilamide, J. A. M. A. **109**:12 (July 3) 1937. (*b*) Wood, B.: Anemia During Sulfanilamide Therapy, ibid. **111**:1916 (Nov. 19) 1938. (*c*) Erf, L. A., and MacLeod, C. M.: Hemolysis from Sulfapyridine, J. Clin. Investigation **18**:472, 1939.

per cent in adults. He ascribed the anemia in the 21 cases to hemolysis, because of the abrupt appearance of jaundice and urobilinuria. In 8 additional instances a "slow" type of anemia was encountered, which was similar to that previously described by Jennings and Southwell-Sander.[3] Wood was unable to determine whether this type was due to sulfanilamide or to the underlying disease. Erf and MacLeod [2e] have recently reported a regular increase in the rate of hemolysis in patients with pneumonia receiving sulfapyridine.

The present study was made with the purpose of determining the effects of varying doses of sulfanilamide and sulfapyridine on hepatic function and hemoglobin metabolism. We were primarily interested in determining whether the administration of either drug regularly produced evidence of hepatic dysfunction and increased destruction of blood. It was hoped that information would be obtained with respect to whether the occasional occurrence of jaundice and hemolytic anemia represents an accentuation of usual toxic effects or a true drug idiosyncrasy.

MATERIAL AND METHODS

During the past two years we have recorded the therapeutic activity of sulfanilamide in 110 and of sulfapyridine in 44 cases of various types of infection. Sixteen cases of distinct or marked jaundice were observed; all the patients were in the group receiving sulfanilamide. Although this will convey some idea of the frequency of jaundice after sulfanilamide therapy, the figures just given cannot be looked on as representing a true incidence. The great majority of the 110 patients treated were in the medical service of the University Hospital. Several of the patients with jaundice, however, were in the surgical service or other services, and while we have seen all of the jaundiced patients, we recognize that an indeterminate number of patients not included in our records have been treated with sulfanilamide. While the number of sulfapyridine-treated patients is an exact total, therapy had to be abandoned early in a considerable percentage of instances because of nausea and vomiting. Therefore, although we have encountered no instances of jaundice following administration of sulfapyridine, it is realized that the number of patients given the substance in the doses usually effective is too small to permit definite conclusions.

The data to be presented were obtained from two groups of cases. 1. The first was composed of 8 patients who were selected for study prior to the administration of sulfanilamide or sulfapryidine. The nature of the infection in these cases was such that therapy could be postponed for a number of days, during which control observations were made. Various determinations were made before, during and after administration of the drug. They included determination of the value for plasma bilirubin; of the urobilinogen content of a twenty-four hour sample of urine; of the per diem amount of urobilinogen in the feces for consecutive four day periods; of the levels of free and total sulfanilamide or sulfapyridine in the blood; of the hemoglobin content; of the number of erythrocytes, and of the percentage of reticulocytes. The value for urinary coproporphyrin was determined in 4 of the 8 cases. 2. The second group of patients numbered 28. The data

3. Jennings, G. H., and Southwell-Sander, G.: Anemia and Agranulocytosis During Sulfanilamide Therapy, Lancet **2**:898, 1937.

obtained from this group are less complete and vary in extent in different instances. The study in these cases was not planned as it was for the patients in group 1; consequently the various observations which will be noted were usually made only after administration of the drug had been commenced and often only after the development of definite jaundice or anemia. This group is composed chiefly of cases in which jaundice appeared after administration of sulfanilamide; in 3 of the cases, as will be noted subsequently, the drug was placed in the peritoneal cavity at the time of operation in the hope of preventing peritonitis following perforation in the gastrointestinal tract. Observations are included in which there was evidence of reduced hepatic function without jaundice; also, cases are included in which smaller doses of the drug were without untoward effect on the liver or on the blood.

Two additional cases of icterus were omitted because of the likelihood that pulmonary infarction was present. Both of the patients suffered from patent ductus arteriosus and vegetative endocarditis.

The following methods were employed: The blood sulfanilamide and sulfapyridine levels were determined by the method of Marshall and Litchfield.[4] The urobilinogen content of the urine and feces was determined by the Terwen[5] method as modified by Watson.[6] The normal range of values with this method are 0 to 3 mg. per day for the urine and 40 to 280 mg. per day for the feces. The urinary coproporphyrin was estimated in twenty-four hour samples of urine by means of the procedure described by Fikentscher,[7] slightly modified.[8] This method depends on ether extraction of the acid urine, removal of the coproporphyrin with dilute hydrochloric acid and quantitative determination by measurement of the intensity of red fluorescence excited by ultraviolet rays. The measurement is made with a Zeiss *Stufenphotometer* and a standard coproporphyrin solution. It is believed that the normal range with this method is 30 to 100 γ per day. The value for plasma bilirubin was determined by the Jendrassik and Czike[9] modification of the van den Bergh method.[10] The Zeiss

4. Marshall, E. K., Jr., and Litchfield, J. T., Jr.: The Determination of Sulfanilamide, Science **88**:85, 1938.

5. Terwen, A. J. L.: Ueber ein neues Verfahren zur quantitative Urobilin Bestimmung in Harn und Stuhl, und über die Bereitung und die Eigenschaften von einem möglichst reinem Urobilinpräparat, Deutsches Arch. f. klin. Med. **149**: 72, 1925.

6. Watson, C. J.: (*a*) Studies of Urobilinogen: I. An Improved Method for the Quantitative Estimation of Urobilinogen in Feces and Urine, Am. J. Clin. Path. **6**:458, 1936; (*b*) II. The Per Diem Excretion of Urobilinogen in Urine and Feces by Normal Individuals, and by Patients Having Diseases Not Primarily Affecting the Liver or Biliary Tract, Arch. Int. Med. **59**:196 (Feb.) 1937; (*c*) III. The Per Diem Excretion of Urobilinogen in the Common Forms of Jaundice and Liver Disease, ibid. **59**:206 (Feb.) 1937.

7. Fikentscher, R.: Quantitative Porphyrin—Bestimmung durch Lumineszenzintensitätsmessung mit dem Stufenphotometer, Biochem. Ztschr. **149**:257, 1932.

8. Details of this modification will be described elsewhere.

9. Jendrassik, A. C., and Czike, A.: Bestimmung des Bilirubins im Blute, Ztschr. f. d. ges. exper. Med. **60**:554, 1928.

10. In accordance with an observation made by Dr. I. J. Pass, working in this laboratory, that maximum coupling is effected only if larger amounts of sodium nitrite are used in diazotizing the sulfanilic acid, we have employed 0.4 cc. of 0.5 per cent sodium nitrite for each 9.6 cc. of 0.5 per cent sulfanilic acid, rather than 0.1 cc. as recommended by Jendrassik and Czike.[9]

Stufenphotometer was employed as recommended by Heilmeyer and Krebs.[11] Because of the considerable variation in hepatic function,[12] the upper limit of normal is somewhat arbitrary; for the great majority of normal persons the range is from 0.30 to 1.0 mg. per hundred cubic centimeters. The value for hemoglobin was determined in terms of grams per hundred cubic centimeters by means of the Sheard-Sanford photelometer.[13] Reticulocytes were counted in dry smears prepared in the following manner: Thin, uniform smears of a 1 per cent alcoholic solution of brilliant cresyl blue were made on ordinary glass slides. As soon as these were dry, very thin blood smears were superimposed on the dye in the usual way; the wet smears were at once placed in a moist chamber (a Petri dish or a staining jar containing wet filter paper on the bottom). After ten minutes the smears were removed and rapidly dried by whipping. They were not counterstained, since we have noted a regular lowering of the reticulocyte percentage when this is done. With this method the normal range is from 0.5 to 1.5 per cent. Data relating to the size and hemoglobin content of the erythrocytes were obtained by means of the Wintrobe hematocrit tube[14] and the Pijper halometer (Zeiss).

RESULTS

The data for the 8 cases in group 1 have been recorded graphically and are shown in charts 1 to 6 inclusive. The clinical data and laboratory findings in the cases of group 2 are given in table 1. Additional data relating to the erythrocytes are given in table 2.

COMMENT

Hemoglobin Metabolism.—This may be defined as the relation between the rates of blood destruction and blood regeneration as measured by the output of urobilinogen in the feces and the reticulocyte percentage.[12] Evidence of increased hemoglobin metabolism was noted in all cases in which data were obtained relative to the rate of blood destruction and regeneration. A varying degree of increase of urobilinogen in the feces and of the reticulocyte percentage is noted in the data for cases 1 to 8, inclusive (charts 1 to 6). A marked increase of urobilinogen in the feces was likewise noted in cases 20 and 25 (table 1), in both of which the hemoglobin and erythrocyte levels rapidly declined. Increases in serum bilirubin and urine urobilinogen which occurred are regarded as chiefly due to hepatic dysfunction and will be considered

11. Heilmeyer, L., and Krebs, W.: Spektrophotometrische Untersuchungen des Ehrlich-Pröscherschen Bilirubin—Azofarbstoffes und ihre praktische Anwendung, besonders zur quantativen Bestimmung des Bilirubins im Blutserum, Biochem. Ztschr. **223**:352, 1930.

12. Watson, C. J.: The Pyrrol Pigments with Particular Reference to Normal and Pathologic Hemoglobin Metabolism, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 4, p. 2445.

13. Manufactured by the Central Scientific Co.

14. Wintrobe, M. M.: The Size and Hemoglobin Content of the Erythrocyte: Methods of Determination and Clinical Application, J. Lab. & Clin. Med. **17**: 899, 1932.

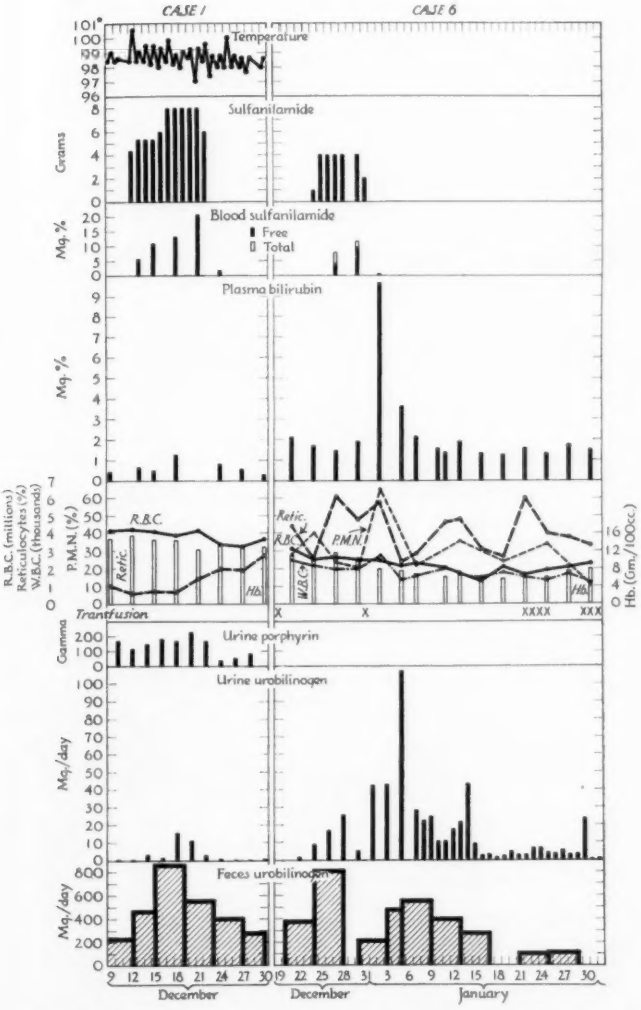

Chart 1.—Records of L. G., a man aged 54 (case 1), and K. B., a woman aged 48 (case 6). In the case of L. G. there was chronic brucellosis of eight months' duration. Marked improvement followed sulfanilamide therapy. In the case of K. B. there was probable subleukemic splenic reticuloendotheliosis. Sulfanilamide therapy was given for gluteal abscess following injection of liver extract.

in this relation later. Exact correlation of the time of appearance and duration of increased hemolysis with the dosage and with the blood level of sulfanilamide was not possible because of varying lag in excretion of urobilinogen in the feces. This is a variable which is incident to the rate at which the feces traverse the intestinal tract. It is best

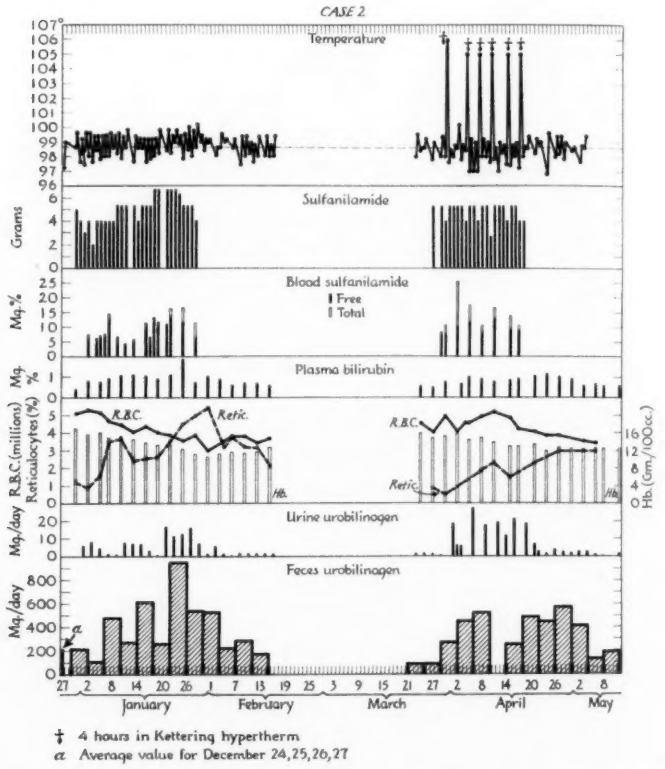

Chart 2 (case 2).—Record of J. F., a man aged 37. There was chronic brucellosis (duration three years). No improvement followed sulfanilamide therapy or sulfanilamide plus fever therapy.

illustrated in case 8 (chart 5), in which constipation interfered with regular collection of feces. In this instance the amounts of urobilinogen noted for the four day periods ending on March 30 and April 3 were very small, probably because of the very small amounts of feces obtained by means of repeated enemas. In the next period (April 4 to 6), however, the bowel movements were spontaneous and regular, and a very

large amount of urobilinogen was noted in the feces. There can be no doubt that part of this, at least, represented destruction of blood which had occurred during the earlier periods. For this reason an average value for the three periods is recorded.

In general, it is evident from the data on the 8 cases in group 1 (charts 1 to 6) that increased hemolysis of some degree appeared within

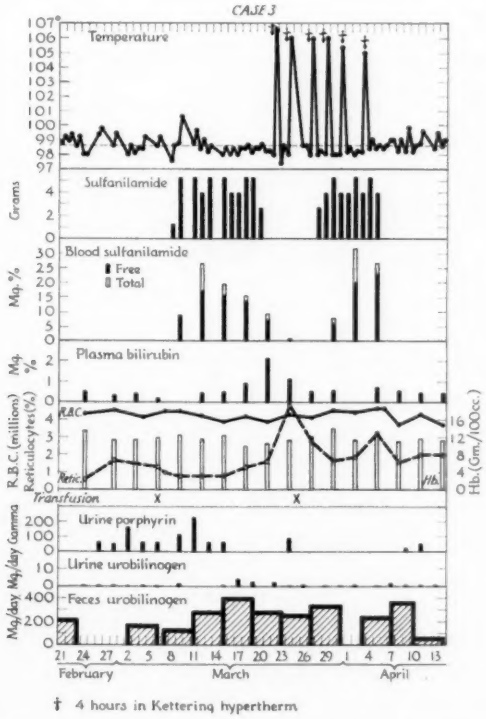

Chart 3 (case 3).—Record of W. R., a man aged 31. There was chronic gonorrheal arthritis. Improvement followed sulfanilamide plus fever therapy.

four to eight days after administration of sulfanilamide or sulfapyridine, that it was usually most marked with higher blood levels of the drug or soon after the occurrence of such levels and that it subsided within a few days after administration had been discontinued. One exception has been noted in respect to time of subsidence; this was in case 2 (chart 2). It is of considerable interest that in this case the urobilinogen content of the feces became markedly elevated during sulfanilamide

therapy, returning to normal within six days after administration of the drug was stopped. In a later period, a combination of sulfanilamide and fever therapy resulted in a second elevation of urobilinogen in the feces, and the increased hemolysis persisted this time for sixteen days. The cause of this persistence was not determined. The data in general do not suggest that fever produces any increase in the hemolytic action of the drugs. Treatment with artificially induced fever combined with

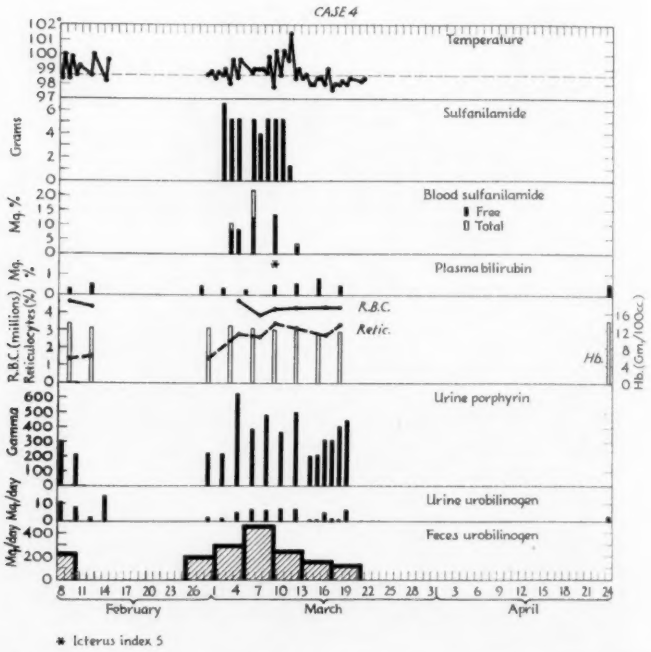

Chart 4 (case 4).—Record of C. D., a man aged 39. There was chronic rheumatoid arthritis. No improvement followed sulfanilamide therapy.

sulfanilamide in another instance (case 3 [chart 3]) was not associated with any greater increase of hemolysis than was noted as following administration of sulfanilamide alone.

A comparison of the effect on blood destruction of relatively large and small amounts of the drug during different periods has been carried out in but 1 instance (case 7). The patient received sulfapyridine. In chart 6 it may be noted that the value for urobilinogen in the feces reached 744 mg. per day within six days after a blood sulfapyridine level of 10.2 mg. per hundred cubic centimeters had been attained. The use

of the drug was discontinued for five days and then resumed with smaller doses (1.5 Gm. daily for four days). At the end of this period the blood level was 6.2 mg. per hundred cubic centimeters. This was associated with a mild increase of hemolysis lasting at least through

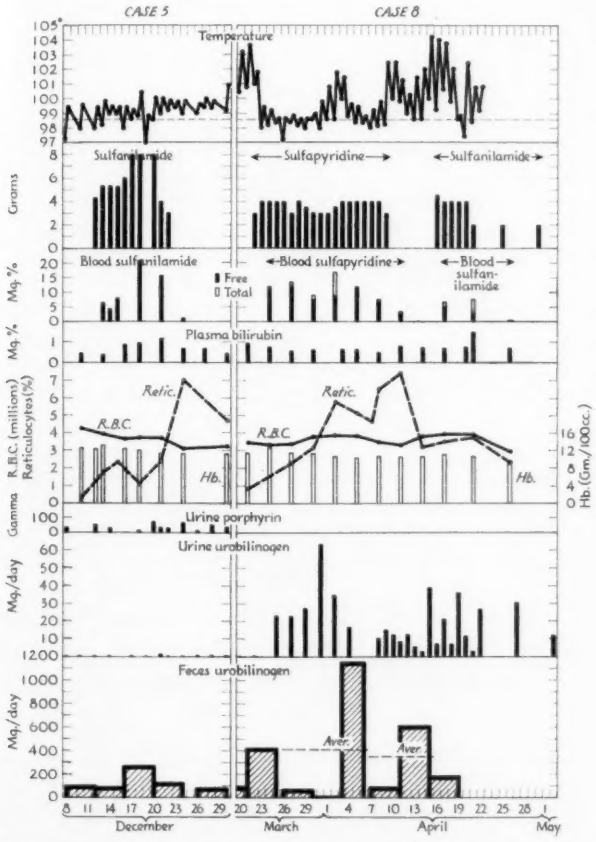

Chart 5.—Records of E. S., a girl aged 17 (case 5), and B. B., a man aged 32 (case 8). In the case of E. S. there was low grade chronic rheumatic fever. The patient was unimproved after sulfanilamide therapy. In the case of B. B. there was subacute bacterial (Streptococcus viridans) endocarditis. The patient was unimproved after sulfanilamide and sulfapyridine therapy. The significance of the averages indicated by the broken line is discussed in the text.

Jan. 11, 1939. From January 19 until February 6, 0.5 Gm. was given daily. During this period the fecal urobilinogen remained at low normal levels, and there was no further evidence of increased hemolysis.

The fact that administration of sulfapyridine is followed by increased blood destruction (cases 7 and 8) is believed to be of significance with respect to the question of the possible relation of methemoglobinemia to increased output of urobilinogen in the feces. In neither case 7 nor case 8 was cyanosis observed. Although examination of the blood for methemoglobin was omitted, we believe that the absence of cyanosis excludes the presence of any appreciable degree of methemoglobinemia.[15] We have rarely observed methemoglobinemia in our patients receiving

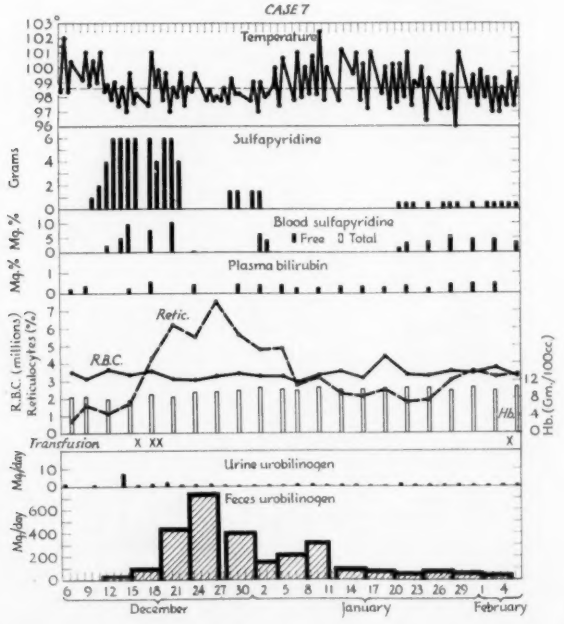

Chart 6 (case 7).—Record of R. K., a woman aged 25. Subacute bacterial (viridans) endocarditis was present. Temporary improvement followed sulfanilamide therapy.

sulfapyridine. Thus, it is highly unlikely that methemoglobinemia bears any relation to increased hemolysis. This, of course, is also borne out by the frequent observation of marked cyanosis following administration of sulfanilamide without development of any appreciable degree of anemia.

15. Watson, C. J.; Vigness, I., and Spink, W. W.: Relation of Methemoglobin to the Cyanosis Observed After Sulfanilamide Administration, Proc. Soc. Exper. Biol. & Med. **40**:547, 1939.

The values noted in case 6 (chart 1) require particular mention. It is seen that mild hemolytic anemia of macrocytic type was present prior to sulfanilamide therapy. This was of the type not infrequently associated with leukemia and reticuloendotheliosis.[16] Shortly after sulfanilamide therapy was commenced the urobilinogen content of the feces increased, and the anemia became much more marked. The use of the drug was discontinued, after which there was rapid decrease in jaundice, although the anemia gradually increased in association with a persistent elevation of the value for urobilinogen in the feces. This persistence of increased hemolysis is regarded as part of the underlying disease; it may be pointed out that the values recorded for January 25 and 29 are still elevated when the total amount of circulating hemoglobin is considered.[12] By that time, however, the rate of blood destruction had decreased sufficiently so that the increased reticulocyte percentage resulted in a distinct increase of hemoglobin and erythrocytes.

It is noteworthy that the patient in case 6 exhibited marked neutropenia prior to use of sulfanilamide but that prolonged administration of the drug was not productive of any appreciable further decrease of the neutrophils.

The data in cases 1 to 8 indicate that the degree of anemia is dependent primarily on the degree of increased hemolysis and secondarily on the reticulocyte response. The major drop in hemoglobin and red blood cells is seen to be related closely to the periods in which the largest amounts of urobilinogen were found in the feces. In general, there is evident correlation between the degree and duration of the anemia and the extent of the reticulocyte response. In case 7 (chart 6), in which the reticulocyte response was relatively marked, no decline in the hemoglobin level occurred. In case 5 (chart 5) an unexplained discrepancy was noted between the values for reticulocytes, hemoglobin and feces urobilinogen. The last-mentioned value was slightly increased during the period from December 16 to 20. A slight decline in the level of hemoglobin followed, and the percentage of reticulocytes then rose to 7. In spite of this evidence of active regeneration, the hemoglobin level did not increase, although the urobilinogen determinations failed to reveal evidence of blood destruction. It is possible, of course, that more than the usual absorption of urobilinogen in the intestine was taking place in this instance, and if this were true the rate of blood destruction would have been more rapid than was apparent.

Although it is clear from the foregoing facts that some degree of increased blood destruction may follow administration of sulfanilamide

16. Watson, C. J.: Hemolytic Jaundice and Macrocytic Hemolytic Anemia: Certain Observations in a Series of Thirty-Five Cases, Ann. Int. Med. **12**:1782, 1939.

TABLE 1.—*Clinical and Laboratory Data in Group 2*

Case No., Patient Sex, Age	Diagnosis and Complications	Amount of Sulfanilamide, Periods Given, and Blood Level: Amount per Day	Level of Free Sulfanilamide	Date	Icterus Index or Serum Bilirubin	Date	Van den Bergh Test	Urine Urobilinogen, Mg. per Day	Date	Hemoglobin, % (Sahli)	Date	Red Blood Cells, Millions per Cubic Mm.	Date	Comment
					I.I.			25.7	12/17	81	12/11	....	.....	Icterus noted on 12/15; had
9	Bronchopneumonia and	12/12 to 12/14	17.5	12/13	14	12/15	PD	1.3	12/19	64	12/17	....	.....	disappeared by 12/19; recovery
J. M.	hemolytic streptococcus empyema	7 Gm.			8	12/19								after several weeks of fever
F														
23														
10	Hodgkin's disease; in-	7/5	2.3	7/11	...	.....	.....	6.2	7/ 4	66	7/ 7	....	.....	Hodgkin's disease relatively
M. F.	tercurrent pyelo-	0.33 Gm.	2.6	7/14	...	...	.....	4.5	7/ 5	65	7/16	....	.....	quiescent (laminectomy for cord
F	nephritis	7/6 to 7/16	...	....	...	.....	.....	0.7	7/ 6	..	.....	....	.....	involvement in 1936); no
29		1.33 Gm.						4.6	7/ 7	..	.....	....	.....	icterus during sulfanilamide
		7/16						2.8	7/ 9	..	.....	....	.....	therapy
		0.33 Gm.						1.6	7/11	..	.....	....	.....	
								3.2	7/13	..	.....	....	.....	
								4.1	7/15	..	.....	....	.....	
								3.9	7/17	..	.....	....	.....	
11	Carcinoma of stom-	10 Gm. of	7.2	5:15 p.m. 2/4	88	2/9	PD	10.9	2/14	68	2/ 3	....	.....	No icterus prior to operation;
L. M.	ach; perforation; peri-	crystals placed	15.1	9:00 p.m. 2/4	103	2/13	PD	....	.....	59	2/ 9	....	.....	first noted 2/6; rapidly became
M	tonitis; laparotomy	in peritoneal	6.6	11:00 p.m. 2/5	122	2/15	PD	....	.....	72	2/13	....	.....	intense; seven blood trans-
59	and closure of per-	cavity at oper-	Trace	9:00 p.m. 2/6										fusions (400-1,000 cc.) 2/4 to
	foration	ation, 2:15 p.m., 2/4/39												2/13; died 2/16
12	Bowel obstruction;	12 Gm. of	20.8	12/26	243	12/26	PD	14.4	12/30	88	12/26	....	.....	No icterus prior to operation;
H. L.	laparatomy; acciden-	crystals placed	15.0	12/28	361	12/28	PD	....	.....	76	12/30	....	.....	first noted 12/25; rapidly became
M	tal perforation	in peritoneal	6.3	12/29	240	12/29	PD	....	.....	..	.....	....	.....	intense; 800 cc. blood trans-
44		cavity at operation on 12/24; 2 Gm. subcutaneously on 12/25 and 12/26	3.5	12/30	203	12/30	PD	....	.....	..	.....	....	.....	fusion on 12/24; 1,600 cc. on 12/25; 600 cc. 12/30; died 12/31
13	Subacute bacterial	7/17 to 8/19	7.8	7/21	6	7/14	.....	0.7	7/16	45	7/13	....	.....	Seventeen blood transfusions,
L. R.	(viridans) endocar-	4 Gm.	9.0	7/25	2.2	8/ 2	.....	1.0	7/20	35	7/20	....	.....	100 to 400 cc.
F	ditis; old rheumatic		10.6	7/28	...	.....	.....	6.5	7/22	47	7/22	....	.....	
29	mitral valve defect				S.B.									
			13.2	8/ 1	...	.....	.....	2.6	7/24	52	7/25	....	.....	
			13.0	8/ 4	...	.....	.....	0.5	7/25	56	8/ 3	....	.....	
			11.0	8/ 8	...	.....	.....	1.4	7/30	63	8/ 5	....	.....	
			4.0	8/15	...	.....	.....	0.7	7/31	68	8/23	....	.....	
			6.0	8/16	...	.....	.....	0.5	8/ 3	..	.....	....	.....	
								21.8	8/ 5	.	.....	....	.....	
								49.0	8/ 8	..	.....	....	.....	
								22.5	8/10	..	.....	....	.....	
								26.0	8/12	..	.....	....	.....	
								31.0	8/14	..	.....	....	.....	

					I.I.									
14	Probable bacillary	12/20 to 12/21	9.0	12/22	7	12/14	.....	3.7	12/22	81	12/ 5	2.7	12/27	Continuous irregular fever; no
A. M.	dysentery; cecal ab-	5 Gm.	....	.....	9	12/22	.....	....	.....	79	12/ 7	....	.....	diarrhea during period of ob-
F	scess; B. coli septi-	12/31	....	.....	7	12/28	.....	....	.....	64	12/21	....	.....	servation; many blood trans-
31	cemia	5 Gm.	....	.....	32	1/ 4	PD	....	.....	45	12/27	....	.....	fusions between 12/20 and 1/12;
					28	1/12	PD	.. .	.....	55	1/ 4	....	.....	died 1/14
					22	1/13	.....	....	.....	80	1/13	....	.....	
15	Acute benign lymphad-	6/22 to 6/24	7.4	6/24	17.0	6/24	PD	18.5	6/26	..	.....	....	.....	Jaundice noted 6/27; fever per-
L. S. F.	enosis (infectious	13 Gm.	....	.....	...	.....	.....	21.6	6/28	..	.....	....	.....	sisted through 7/4, much less
F	mononucleosis)	6/25	. ..	.....	...	.....	.....	1.7	6/30	..	.....	....	.....	after 7/1; urticarial rash 6/28;
22		4 Gm.	....	.....	...	.....	.....	1.5	7/ 1	..	.....	....	.....	no improvement noted after
		6/26	....	.....	...	.....	.....	1.0	7/ 5	..	.....	....	.....	sulfanilamide
		3 Gm.	....	.....	...	.....	.....							
16	Carcinoma of cervix;	11/14	....	.....	16	11/ 9	PD	....	.....	52	10/28	3.96	10/28	Slight icterus noted prior to
I. P.	peritonitis following	3 Gm.	....	.....	45	11/18	PD	....	.....	36	11/ 7	3.12	11/ 7	therapy; marked increase
F	high voltage roent-	11/15 to 11/18	....	.....	13	11/22	PD	....	.....	39	11/ 9	3.5	11/ 9	after sulfanilamide; rapid
31	gen therapy	4 Gm.	....	.....	...	.....	.....	....	.....	54	11/15	3.6	11/30	disappearance when discon-
										68	11/30	....	.....	tinued; roentgen therapy com-
										84	1/11	....	.....	menced on 11/7; repeated blood
														transfusions 11/6 to 11/17
17	Prostatic obstruction;	1/6 to 1/17	12.4	1/8	23	1/14	PD	++	1/17	74	1/ 1	....	.....	Jaundice first noted on 1/14;
C. A.	pyelonephritis; trans-	4 Gm.	7.2	1/10	12	1/16	.....	....	.....	68	1/17	....	.....	discharged on 3/3/38, much
M	urethral resection		4.2	1/14	10	1/21	.....	....	.....	73	2/ 2	....	.....	improved
64														
					S.B.									
18	Recurrent gonorrheal	8/3 to 8/16	2.4	8/ 8	0.73	8/ 2	.....	1.8	8/ 1	87	7/29	....	.....	No jaundice; discharged mark-
G. P.	arthritis	4 Gm.	5.7	8/ 9	0.64	8/13	.....	8.6	8/ 3	75	8/ 7	....	.....	edly improved on 8/19/38
M			7.8	8/15	...	.....	.....	3.5	8/ 5	78	8/10	....	.....	
40								15.3	8/ 7	75	8/13	....	.....	
								7.3	8/ 9	75	8/16	....	.....	
								19.4	8/11					
								10.2	8/13					
					I.I.									
19	Hemolytic streptococ-	2/18 to 2/22	....	.....	32	3/15	PD	5.6	3/17	81	3/14	....	.....	Continuous marked septic
M.C.	cus septicemia (from	4 Gm.	....	.....	68	3/17	.....	....	.....	79	3/16	....	.....	fever; no improvement after
F	infected wound);	3/11 to 3/14	....	.....	...	.....	.....	....	.....	76	3/17	....	.....	sulfanilamide; progressively
54	secondary cellulitis;	4 Gm.	....	.....	...	.....	.....	....	.....	71	3/18	....	.....	deepening jaundice; died 3/19/39
	jaundice with enlarged liver	9 Gm. (total) between 3/17 and 3/19, inclusive												
20	Chronic osteomyelitis;	5/23 to 5/27	....	.....	10	5/30	Indirect	307.0	5/31	61	5/17	....	.....	Negative blood cultures; jaun-
F. S.	acute exacerbation;	5.3 Gm.	....	.....	...	.....	.....	73.5	6/ 1	32	5/27	....	.....	dice noted on 5/26; had dis-
M	sequestrectomy		....	.....	...	.....	.....	58.6	6/ 2	41	5/29	....	.....	appeared by 5/30; reticulocytes
44			....	.....	...	.....	.....	25.1	6/ 3	61	5/31	....	.....	2.2% on 5/29; feces urobilinogen
								7.5	6/ 4	84	6/ 8	....	.....	markedly elevated; 813.8 mg.
								10.7	6/ 5	85	6/13	....	.....	per day, 5/27 to 5/31; marked
								5.1	6/ 6	..	.....	.. .	.....	improvement after discontinu-
								1.6	6/15	..	.....	....	.....	ance of drug; continuous marked fever until 5/30

TABLE 1.—*Clinical and Laboratory Data in Group 2—Continued*

Case No., Patient Sex, Age	Diagnosis and Complications	Amount of Sulfanilamide, Periods Given, and Blood Level: Amount per Day	Level of Free Sulfanilamide	Date	Icterus Index or Serum Bilirubin	Date	Van den Bergh Test	Urine Urobilinogen, Mg. per Day	Date	Hemoglobin, % (Sahli)	Date	Red Blood Cells, Millions per Cubic Mm.	Date	Comment
21	Pneumonia; empyema	12/11 to 12/19	4.3	12/13	20	12/19	PD	....	.....	86	12/ 6	....	.....	Sulfanilamide discontinued on
N. M		4 Gm.	2.7	12/16	24	12/21	PD	....	.....	78	12/21	....	.....	12/19 because of appearance of
M			6.9	12/17	10	12/28	.....							jaundice; no improvement;
21			7.0	12/19	...	.....	.....							continuous septic fever; died
22	Epididymitis; hemo-	3/17 to 3/22	6.0	3/22	29	3/23	Biphasic	....	.....	66	3/16	2.7	3.16	Sulfanilamide discontinued
G. M.	lytic streptococcus	4 Gm.	7.0	3/23	21	3/24	PD	....	.....	65	3.16	2.3	3.16	because of icterus; epididymitis
M	recovered from blood;		6.2	3/24	7	3/31	.....	....	.....	55	3/30	2.0	3.30	and bacteremia disappeared;
78	hypertension; cere-		....	.....	8	4/ 6	.....	....	.....	50	4/ 4	....	.....	fever diminished in spite of
	bral and coronary		....	.....	...	.....	.....	....	.....	40	4/12	....	.....	increasing stupor; decubitus
	arteriosclerosis		....	.....	...	.....	.....	....	.....	35	4/15	....	.....	ulcers
23	Squamous cell carci-	3/3 to 3/8	9.0	3/ 4	5	2/27	.....	39.7	3/ 8	51	3/ 2	3.91	3/ 6	Jaundice noted on 3/6; patient
G. W.	noma (cervix) with	6 Gm.	14.0	3/ 6	27	3/ 6	PD	....	.....	55	3/ 6	2.0	3/13	irrational and very toxic on
F	pulmonary and pleural				S.B.									3/7; spiking fever; blood trans-
44	metastases; empyema;	3/9 to 3/10	....	.....	3.4	3/ 7	.....	....	.....	32	3/13	....	.....	fusions on 3/13 and 3/14; rib
	hemoptysis	3 Gm.	....	.....	...	.....	.....	....	.....	48	3/15	....	.....	resection, biopsy 3/10
										54	3/17			
24	Pyonephrosis; nephrec-	4/15	....	.....	4.76	4/24	PD	61.8	4/24	52	4/24	2.8	4/24	Marked improvement
R. H.	tomy	3.6 Gm.	....	.....	1.27	4/27	.....	39.3	4/25	49	4/27	2.5	4/27	
M		4/16	....	.....	1.06	4/30	PD	25.4	4/27	54	5/ 1	3.4	5/1	
61		3.3 Gm.	....	.....	...	.....	.....	32.5	4/29					
		4/18 to 4/23	....	.....	...	.....	.....	1.1	5/ 1					
		1.3 Gm.	....	.....	...	.....	.....							
					I.I.									
25	Toxic hepatitis fol-	4/15 to 4/18	Trace	4/23	50	4/22	PD	87.3	4/25	68	4/24	3.68	4/24	Slight icterus said to have
R. N.	lowing pneumonia;				S.B.									been present before sulfanil-
M	sulfanilamide given by	6.6 Gm.	....	.....	8.4	4/24	PD	221.1	4/27	59	4/27	3.28	4/27	amide; marked jaundice first
	local physician because				I.I.									noted on 4/19; feces urobili-
	of recurrence of fever on	(total)	....	.....	40	4/25	PD	41.7	4/30	49	4/30	3.06	5/ 3	nogen in mg. per day:
	4/15, three days after				S.B.									129 4/25
	effective use of anti-		....	.....	3.3	4/27	.....	86.4	5/ 2	46	5/ 3	2.7	5/ 6	693 4/29
	pneumococcic serum				I.I.									404.5 5/ 3
	for type III pneu-		....	.....	20	4/27	.....	....	.....	45	5/ 6	3.2	5/ 9	327 5/ 8
	monia				S.B.									94.8 5/11
			....	.....	1.6	4/30	PD	....	.....	45	5/ 9	4.6	5/15	152.5 5/15
					I.I.									
					11	5/ 1	.....	....	.....	51	5/12			
										58	5/15			
					S.B.			1.4	3/ 2	76	2/28	4.4	2/28	No icterus; collections of feces
26	Pyelonephritis	3/12	7.7	8 a.m. 3/16	0.9	2/28	.....	0.5	3/ 9	65	3/ 9	4.3	3/ 9	for urobilinogen determination
E. P.		1.3 Gm.	8.6	10 a.m. 3/16	0.57	3/12	.....	tr.	3/11	68	3/12	4.1	3/12	were prevented because of
F		3/13	7.7	3/24	0.74	3/15	.....	0.3	3/13	66	3/15	3.7	3/15	marked constipation and
		2.0 Gm.	10.4	3/27	0.72	3/18	.....	tr.	3/15	62	3/18	3.7	3/18	lack of cooperation
			11.4	3/30	0.52	3/19	.....	0.4	3/17	63	3/21	4.0	3/21	
									3/19	68	3/24	4.1	3/24	

E. P. F		1.3 Gm. 3/13 2.0 Gm.	8.6 7.7 10.4	10 a.m. 3/16 3/24 3/27	0.57 0.74 0.72	3/12 3/15 3/18	....	tr. 0.3 tr.	3/11 3/15 3/15	68 66 67	3/12 3/15 3/18	4.1 3.7 3.7	3/12 3/15 3/18	were prevented because of marked constipation and lack of cooperation
		3/14 2.6 Gm. 3/15 2.0 Gm. 3/16 2.6 Gm. 3/23 1.3 Gm. 3/24 4.0 Gm. 3/25 to 3/27 2.6 Gm. 3/30 2.6 Gm. 4/2 2.6 Gm.	11.4 12.4	3/30 4/ 2	0.52 0.48 0.42 0.59	3/19 3/24 3/27 3/30	....	0.4 tr. 0.4 0.2 0.4 0.3 tr.	3/17 3/19 3/21 3/23 3/25 3/27 3/30	63 68 64 68	3/21 3/24 3/27 3/30	4.0 4.1 3.8 3.9	3/21 3/24 3/27 3/30	
27 E. K. M	Postpneumonic empyema (streptococcic)	1/20 5.6 Gm. 1/21 to 1/22 5.0 Gm. 1/23 to 1/27 6.0 Gm. 1/28 5.0 Gm. 1/30 to 2/15 6.0 Gm.	5.7 8.5 6.7 13.5 7.0 8.4 3.8 5.5 7.9	1/21 1/24 1/27 1/30 2/ 2 2/ 6 2/ 9 2/12 2/15	S.B. 0.41 0.48 0.67 1.22 0.88 1.35 1.01 0.79 0.77 0.33 0.57 0.27	1/19 1/21 1/24 1/27 1/30 2/ 2 2/ 6 2/ 9 2/12 2/15 2/18 2/21	....	52.6 39.6 20.1 42.9 18.4 8.0 23.8 35.1 72.1 3.5	1/19 1/20 1/21 1/22 1/24 1/25 1/26 1/27 1/28 2/8	.. ..	....	....	....	No icterus; recovery after rib resection and drainage on 2/15/39
28 ..... M 49	Post-traumatic (automobile accident) peritoneal abscess; stormy postoperative course; constant irregular fever, diminishing gradually after 2/7	12 Gm. placed in peritoneal cavity at operation 1/25 1/26 4 Gm. IV 1/27 4 Gm. IV 1/28 4 Gm. IV 1/29 8 Gm. IV 1/30 8 Gm. IV 1/31 8 Gm. IV 2/1 8 Gm. IV 2/2 8 Gm. IV	2.5 (15 min.)† 2.9 5.3 5.4 5.9 7.0 6.8 6.7 5.8 3.0 4.9 7.6 6.6 7.0	1/25 30 min.† 1 hr.† 2 hr.† 3 hr.† 5 hr.† 7 hr.† 10 hr.† 1/26 1/27 1/28 1/30 1/31 2/ 3	... ...	....	....	....	....	63 57 58 58	1/28 1/30 2/ 3 2/ 7	....	....	Left hospital much improved on 2/15; repeated blood transfusions 2/2 to 2/6; no icterus at any time

I.I. = icterus index; S.B. = serum bilirubin in mg. per 100 cc.; PD = prompt direct; IV = intravenously.

† Postoperatively.

or sulfapyridine given in adequate therapeutic doses, our data on the size and hemoglobin content of the erythrocytes indicate that the anemia which may result differs from both the familial, or spherocytic, and the secondary, or macrocytic, hemolytic anemias.[16] The most significant difference is in hemoglobin content. Instead of exhibiting a color index of 1 or above, tests revealed a value generally below 1. The color index was elevated in but 1 instance. The patient (case 22) had mild macrocytic anemia before sulfanilamide therapy was commenced. In case 2 the color index was 1.0, but this declined to 0.89 during the second period of therapy, when the hemoglobin level had again fallen. In case 6 it is perhaps noteworthy that the color index fell from 1.06 to 0.95

TABLE 2.—*Data on Size and Hemoglobin Content of Erythrocytes in Various Instances*

Case No.	Date	MCV	MCH	MCC	MCD	Color Index	Hematocrit, Per Cent
2	2/15	116.7	34.8	30.0	8.4	1.0	42.9
	4/ 5	100.7	31.2	31.1	8.2	0.92	46.0
	4/27	112.4	32.8	29.2	8.4	0.96	43.8
3	2/24	88.4	30.8	34.9	...	0.91	38.7
	3/12	99.3	27.2	27.4	8.1	0.8	42.3
	3/15	106.4	32.2	30.3	8.1	0.94	41.6
	3/18	97.9	23.8	24.3	8.1	0.71	41.1
	3/21	97.2	27.0	27.7	8.3	0.8	38.2
	3/24	93.3	26.9	28.8	8.1	0.8	40.3
4	2/28	101.6	28.6	28.2	...	0.84	44.7
	3/12	102.1	28.0	27.5	8.2	0.83	43.7
	3/18	95.6	27.3	26.1	8.5	0.81	41.4
8	3/21	111.5	33.0	29.6	7.8	0.95	38.8
	4/11	111.1	31.8	28.6	8.2	0.92	37.0
	4/26	116.3	33.4	28.7	8.2	0.95	34.3

MCV = Mean corpuscular volume.
MCH = Mean corpuscular hemoglobin.
MCC = Mean corpuscular hemoglobin concentration.
MCD = Mean corpuscular diameter.

after sulfanilamide therapy, in spite of a marked increase in the rate of blood destruction with increasing jaundice and anemia. While these variations are not regarded as significant in themselves, it is at least evident that the color index did not rise as might have been expected with hemolytic anemias of other causation. Exact data as to size of the erythrocytes were available in cases 2, 3, 4 and 8. This is seen in table 2. The values given in table 2 may be compared with the data for cases 2, 3, 4 and 8, respectively, for the sake of correlation with the results of the other determinations which were made. Although the number of cases studied is limited, the data indicate that the tendency is toward a macrocytic, hypochromic type of anemia. Past experience with the Pijper halometer permits us to conclude that 8.0 microns is the extreme upper limit of normal for mean corpuscular diameter in this vicinity. Our normal range is from 7.5 to 8.0. Thus it is clear that in the 4 cases

just mentioned the mean corpuscular diameter and the mean corpuscular volume are moderately increased, while the mean corpuscular hemoglobin concentration, in conformity with the color index, is slightly reduced.

The tendency to reduction of the color index and of the mean corpuscular hemoglobin concentration suggests that there is, in addition to a heightened destruction of erythrocytes, a disturbance in the formation of hemoglobin. In many other hemolytic anemias, for instance, that due to phenylhydrazine or distilled water, this is not the case, and in these the color index and hemoglobin concentration are high. One condition, however, is very similar, with respect not only to the size and hemoglobin content of the red blood cells but also to pigment metabolism. This is the anemia of lead poisoning, which is likewise characterized by increased destruction of blood with relative reduction of the hemoglobin content of the erythrocytes.[17] It is also of much interest that coproporphyrin III has been found to be excreted in the urine in cases of lead poisoning [18] and after administration of sulfanilamide.[19] This porphyrin, which corresponds in configuration to the hemoglobin series, may possibly owe its formation to a disturbed hemoglobin synthesis.

Our data as regards urinary excretion of coproporphyrin are limited to 4 of the cases of group 1.[20] While the porphyrin determinations in these cases have not yielded information from which definite conclusions can be drawn, they are at least of value in revealing that the effect of sulfanilamide on porphyrin metabolism is by no means a constant one. In case 1 it is seen that a questionably significant rise of urinary porphyrin followed the administration of sulfanilamide and that a marked drop had occurred two days after its discontinuance. This drop was associated with marked clinical improvement, and the patient has remained in good health. The quantitative determination of urinary porphyrin includes the isomeric coproporphyrins I and III but does not

17. Aub, J. C.; Fairhall, L. T.; Minot, A. S., and Reznikoff, P.: Lead Poisoning, Medicine **4**:1, 1925. Hirschfeld, H.: Symptomatische Blutveränderungen, in Schittenhelm, A.: Handbuch der Krankheiten des Blutes und der blutbildenden Organe, Berlin, Julius Springer, 1925, vol. 1, p. 189.

18. Grotepass, W.: Zur Kenntnis des in Harn auftretenden Porphyrins bei Bleivergiftung, Ztschr. f. physiol. Chem. **205**:193, 1932. Fischer, H., and Duesberg, R.: Ueber Porphyrine bei klinischer und experimenteller Porphyrie, Arch. f. exper. Path. u. Pharmakol. **166**:95, 1932. Watson, C. J.: Concerning the Naturally Occurring Porphyrins: IV. The Urinary Porphyrin in Lead Poisoning as Contrasted with That Excreted Normally and in Other Diseases, J. Clin. Investigation **15**:327, 1936.

19. Rimington, C.: Porphyrinuria Following Sulfanilamide: Sulfanilamide Dermatitis, Lancet **1**:770, 1938.

20. Further study of the effect of sulfanilamide on porphyrin metabolism is in progress.

distinguish between them. It is quite possible that the mild increase in porphyrin noted even before administration of sulfanilamide was due to excessive excretion of coproporphyrin I related to mild hepatic dysfunction.[21] Disturbance of hepatic function has been noted in cases of brucellosis.[22]

In case 3 (chart 3) a definite although not marked increase in urinary coproporphyrin is noted, occurring soon after sulfanilamide therapy was commenced. This is of questionable significance, however, since the twenty-four hour amount soon decreased to the level observed before the drug was given. In case 4 (chart 4), an instance of severe rheumatoid arthritis, the value was considerably elevated before treatment with sulfanilamide was commenced. Shortly thereafter a marked further increase was noted, and associated with this a toxic rash of morbilliform type appeared. The use of the drug was discontinued, but the coproporphyrin excretion remained elevated. At the same time the urobilinogen content of the feces returned to normal. It is of interest that no elevation of the serum bilirubin and only a mild increase of the urine urobilinogen occurred in this case. A distinct increase in the rate of blood destruction was noted, however. In case 5 (chart 5) no significant variations in the level of urinary coproporphyrin were noted before, during or after therapy. It may be of importance that in this case relatively little effect was noted on either hemoglobin metabolism or hepatic function.

Hepatic Function.—As has been noted, jaundice has been observed only in the group of patients receiving sulfanilamide. We cannot exclude the possible occurrence of slight elevation of the serum bilirubin in some of the sulfapyridine-treated patients, as we have made frequent determinations in but 2 cases (7 and 8 in group 1). In neither of these cases was there any increase of serum bilirubin, although relatively large doses of the drug were given and blood levels of 10 to 12 mg. per hundred cubic centimeters were attained. In contrast to cases 7 and 8 are cases 1 to 6. Significant elevation of the level of serum bilirubin was noted in 5 of these (all except case 4). In case 8 (chart 5), during administration of sulfapyridine, a sustained level of 8 to 12 mg. per hundred cubic centimeters of blood sulfapyridine was attained without elevation of the serum bilirubin. After an interval, as is shown in chart 5, sulfanilamide was administered, and the serum bilirubin mounted to 1.49 mg. per hundred cubic centimeters.

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21. Watson, C. J.: The Porphyrins and Their Relation to Disease: Porphyria, in Christian, H. A.: Oxford Medicine, New York, Oxford University Press, 1938, vol. 4, chap. 9-a, p. 228.

22. Mettier, S. R., and Kerr, W. J.: Hepatitis and Cholecystitis in the Course of Brucella Infection: Report of a Case, Arch. Int. Med. **54**:702 (Nov.) 1934.

While further investigation is necessary to determine whether sulfapyridine causes jaundice, the present observations reveal that the condition is at least much less common after its use than after the use of sulfanilamide.[22a]

We regard jaundice as an evidence of at least relative dysfunction of the liver. Just as in certain cases of familiar hemolytic anemia the liver remains equal to the task of excreting the increased amount of bilirubin in the bile and jaundice fails to appear,[16] sulfanilamide or sulfapyridine may cause increased hemolysis of considerable degree, with increase of urobilinogen in the feces but without elevation of the serum bilirubin. This is seen in cases 4, 7 and 8. In the 16 cases in which jaundice was noted after sulfanilamide, the van den Bergh reaction was of the direct type, often biphasic. Since there was no question of mechanical obstruction in these instances, the direct van den Bergh reaction may be regarded as concrete evidence of regurgitation jaundice due to damage to the liver.

The regular and often marked elevation of the urobilinogen content of the urine after sulfanilamide therapy is regarded as further evidence of parenchymal damage to the liver. It is clear (chart 5) that even extreme urobilinogenuria may occur without any regurgitation jaundice and even without hepatocellular dysfunction as regards bilirubin excretion (case 8). Although there can be no doubt that increased hemolysis, with resultant increased formation of urobilinogen in the bowel, predisposes to urobilinogenuria, it is believed, as has been stated in detail elsewhere,[12] that some degree of dysfunction of the liver is necessary to the appearance of appreciable increases of urobilinogen in the urine. In 2 cases (3 and 5) significant elevation of the level of serum bilirubin was noted without urobilinogenuria. The reason for this is not clear, but it can only be assumed that certain livers dispose of urobilinogen more readily than of bilirubin. The possibility of a disturbance in the absorption of urobilinogen from the bowel must also be considered.

Fever, either natural or artificial, does not appear to be correlated in any way with elevation of the bilirubin content of the serum or of the urobilinogen content of the urine. In case 2 the values for urine urobilinogen were somewhat higher during the second period, in which sulfanilamide and artificial fever were combined. It is doubtful, however, that the difference between the first and the second period is significant when it is considered that there are many other causes of spontaneous fluctuation in the degree of urobilinogenuria.[23] In case 3

22a. Only 1 instance of jaundice following administration of sulfapyridine has been observed during the nine months since this paper was written. In this period, approximately 150 additional patients have been treated with sulfapyridine.

23. Watson, footnotes 6 *b* and *c* and 12.

no increase occurred in spite of repeated fever treatments plus administration of sulfanilamide.

Although the degree of fever alone is not correlated with evidence of dysfunction of the liver, we have been impressed by the greater frequency with which jaundice and urobilinogenuria have been noted in patients who might be classified as relatively very ill or toxic when given sulfanilamide, as contrasted with patients who were relatively nontoxic. The only instance of outspoken jaundice in group 1 was in case 6 (chart 1); the patient was in a very serious condition and showed slight elevation of the serum bilirubin when administration of sulfanilamide was commenced. A similar sequence of events is noted in case 16 of group 2. Of the 16 patients in group 2 in whom mild to marked jaundice was observed, all were very ill or toxic when administration of the drug was begun. It is noteworthy that extreme degrees of jaundice were noted in cases 11 and 12 (table 1), in both of which sulfanilamide was placed directly in the peritoneal cavity at the time of operation. In these cases it is safe to conclude that hepatic damage of some degree had already occurred before operation, since in both cases there was undoubtedly drainage of damaging substances directly into the portal circulation. Icterus appeared only postoperatively, and the intensity was such that there could be little doubt that sulfanilamide had been an important factor in its development. We consider it unlikely, however, that similarly intense icterus would have developed in the absence of the primary disease. Thus, in case 28 of group 2 (table 1), it may be noted that jaundice did not appear, although an equally large amount of sulfanilamide was placed in the peritoneal cavity and relatively large amounts of the drug were given intravenously after operation. Two differences may explain the absence of jaundice in this case in contrast to the deep jaundice in cases 11 and 12. The first is that the blood level of sulfanilamide did not become elevated to a marked degree as it did in cases 11 and 12. The second difference was that the patients in the latter cases were much more toxic and their infection was not as well localized.

In the medical service sulfanilamide has been given in but 1 case in which distinct jaundice was noted prior to therapy. This was case 20. As is noted in table 1, sulfanilamide had been given to this patient during two four day periods before admission to the University Hospital. At the time of admission the patient was comatose and distinctly jaundiced. The icterus index was 32. Supportive measures were of no avail, and since it appeared evident that the patient would die of hemolytic streptococcus septicemia, more sulfanilamide was given, starting with an initial amount of 4 Gm. It is seen that the icterus index increased to 68 within forty-eight hours. Death occurred on the sixth

day of hospitalization. The relative importance of the infection and of the sulfanilamide in the production of jaundice in this case cannot be determined.

We have not observed any strict correlation of the data for serum bilirubin or urine urobilinogen with those for the free or total blood sulfanilamide or sulfapyridine levels. The values noted in case 3 are of interest in this respect. It is seen that the serum bilirubin rose to 2.17 mg. per hundred cubic centimeters at the end of the first course of therapy. The blood sulfanilamide level had now fallen to 7.7 mg. per hundred cubic centimeters from a peak of 17.4 mg. nine days earlier, at which time the serum bilirubin was at a normal level. A distinct although slight rise of the urine urobilinogen occurred in this first period. During the second period, in which the patient was also subjected repeatedly to artificial fever, the blood sulfanilamide level rose to 23 mg. per hundred cubic centimeters, but there was no increase of either serum bilirubin or urine urobilinogen.

In cases 10 and 26, small doses of sulfanilamide used in treating infections of the urinary tract appeared to exert no influence on the function of the liver. In neither case did jaundice or urobilinogenuria appear. We have not observed jaundice in any adult receiving less than 3 Gm. of sulfanilamide per day, and increases of urinary urobilinogen have not been observed in such instances. It appears, therefore, that there may be some correlation with the amount of the drug given. Our results indicate that when doses of 4 to 8 Gm. of sulfanilamide are given daily, some disturbance of hepatic function may be expected in most instances. The degree of disturbance probably depends on two factors: (1) individual variation in susceptibility to the drug and (2) the toxicity of the underlying disease, particularly the extent of its toxic effect on the liver.

CONCLUSIONS

1. Sulfanilamide in customary therapeutic doses usually causes acceleration of the metabolism of hemoglobin characterized by an increase of urobilinogen in the feces and a varying increase in the reticulocyte percentage. The most marked acceleration of hemoglobin metabolism is represented by the unusual cases in which outspoken hemolytic anemia occurs. This condition is therefore to be regarded as a much more marked degree of a usual toxic effect of the drug. Limited data indicate that sulfapyridine has the same effect as sulfanilamide on hemoglobin metabolism.

2. The occurrence of macrocytic or normocytic, mildly hypochromic anemia after administration of sulfanilamide or sulfapyridine indicates a disturbance in hemoglobin formation in addition to increased hemolysis.

3. In many persons the administration of sulfanilamide in the usual doses is followed by some evidence of dysfunction of the liver, such as urobilinogenuria, elevation of the serum bilirubin or outspoken jaundice. The last-mentioned condition is in part of the regurgitation type, as is evidenced by the frequent occurrence of a direct van den Bergh reaction. Sixteen cases of jaundice following sulfanilamide therapy have been encountered. But 1 instance has been noted in which jaundice followed use of sulfapyridine.[22a] Administration of sulfapyridine has not resulted in any elevation of the serum bilirubin in 2 cases in which frequent determinations were made before, during and after administration of the drug. This is in contrast with the results in the group treated with sulfanilamide, in which significant elevation of the serum bilirubin was usual. Although the data on sulfapyridine are as yet too limited to permit definite conclusions, there is reason to believe that this drug may not be as disturbing to hepatic function as is sulfanilamide.

Progress in Internal Medicine

LIVER AND BILIARY TRACT

A REVIEW FOR 1939

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PHYSIOLOGY OF THE BILE ACIDS

The bile acids are formed in the liver and may be considered the specific secretion of that organ. In consequence they are recognized as the most characteristic constituent of the bile. The literature relative to the metabolism of the bile acids has been summarized in the past by Stadelmann [1] and Whipple [4] and most recently by Sobotka.[5] The recent literature on the chemistry of the bile acids was reviewed in 1936 (Greene [6]). Since the last two reports there has been increasing progress in this field. These studies may be summarized under several different headings: (1) experimental and clinical studies on the effect of diet on the secretion of bile; (2) the postoperative concentration of bile salts in human bile; (3) the excretion of intravenously injected cholates; (4) experimental and clinical studies on the effect of the administration of bile salts on the composition of bile, and (5) the therapeutic use of bile salt preparations.

The first reported observations on the volume and composition of the bile were made on patients in whom biliary fistulas had developed spon-

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1. Stadelmann, E.: Der Icterus und seine verschiedenen Formen nebst Beiträgen zur Physiologie und Pathologie der Gallensecretion, Stuttgart, Ferdinand Enke, 1891.

2 and 3. Footnotes have been deleted.

4. Whipple, G. H.: The Origin and Significance of the Constituents of the Bile, Physiol. Rev. **2**:440-459, 1932.

5. Sobotka, H.: Physiological Chemistry of the Bile, Baltimore, Williams & Wilkins Company, 1937.

6. Greene, C. H.: Liver and Biliary Tract: A Review of Certain Recent Contributions, Arch. Int. Med. **57**: 1039-1054 (May) 1936.

taneously, usually as a result of external rupture of an abscess. A hundred years later the development of modern surgical methods of cholecystotomy and cholecystectomy permitted the study of factors affecting the volume and composition of human bile.

A bile fistula in a patient is not necessarily complete. There usually is associated disease of the liver or of the bile ducts, and it is difficult to regulate the diet and activity of the patient so as to obtain unequivocal results.

Such observations led Douglas,[7] in 1817, and Bidder and Schmidt,[8] in 1852, to the experimental production and study of biliary fistulas in animals. The early bile fistulas were complicated by the presence of the gallbladder, which may influence markedly the character of the bile drainage. Even when the gallbladder was removed and associated infection avoided, McMaster, Brown and Rous [9] found marked and inexplicable variation in the daily output of bile.

Kocour and Ivy [10] report that by further improvements in the detail of the methods of collecting bile they have been able to obtain consistent and reproducible results under similar experimental conditions. They used female dogs and prepared their bile fistulas by a modification of the method of Rous and McMaster.[11] During the experimental period continuous suction was applied to the fistula tube to prevent possible blocking. Using this method, Kocour and Ivy [10] report that under similar experimental conditions the secretion of bile did not vary more than 4 per cent. They report that the volume of bile secreted by the liver under controlled experimental conditions is as constant as the secretion of any of the external secretory glands.

The secretion of bile varied with the diet and the amount of bile returned to the intestine. It was lowest (6 to 10 cc. per kilogram per day) when the animal was fasting and there was no return of bile. On a mixed diet but without return of bile the output ranged from 13 to 18 cc.

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7. Douglas, L.: Operations on the Liver and Other Secreting Glands, M. Repository **4**: 283-286, 1817.

8. Bidder, F., and Schmidt, C.: Die Verdauungssäfte und des Stoffwechsel, Leipzig, G. A. Reyher, 1852.

9. McMaster, P. D.; Brown, G. O., and Rous, P.: Studies of the Total Bile: I. The Effects of Operation, Exercise, Hot Weather, Relief of Obstruction, Intercurrent Disease, and Other Normal and Pathological Influences, J. Exper. Med. **37**:395-420, 1923.

10. Kocour, E. J., and Ivy, A. C.: The Effect of Certain Foods on Bile Volume Output Recorded in the Dog by a Quantitative Method, Am. J. Physiol. **122**:325-346, 1938.

11. Rous, P., and McMaster, P. D.: A Method for the Permanent Sterile Drainage of Intra-Abdominal Ducts, as Applied to the Common Duct, J. Exper. Med. **37**: 11-19, 1923.

per kilogram per day, whereas on a mixed diet with a return of a standard amount of bile to the intestine it ranged from 24 to 27 cc. per kilogram per day.

Hot weather had no effect on the volume of the bile when the appetite was unimpaired. The drinking of water or the intravenous injection of 0.5 per cent sodium chloride solution likewise was without effect.

Mixed diet stimulated the output of bile, and meat was the most potent food, whether taken alone or added to a mixed diet. Beef liver was more effective than muscle or beef heart. Olive oil increased the output of bile in fasting dogs, but this effect was not observed when the dose was repeated or when the oil was added to a mixed diet. Dextrose administered to a fasting animal produced a 20 to 30 per cent decrease in the output of bile. When dextrose was added to a mixed diet, there was no characteristic change in the secretion of bile. However, if the secretion of the liver was stimulated by the giving of bile, and dextrose was then injected intravenously, the secretion of bile was increased.

The most marked increases in the volume of the bile followed the administration of bile. Because of greater concentration of bile acids, bile from the gallbladder was a stronger stimulant than bile from the hepatic ducts.

Schmidt, Beazell, Berman, Ivy and Atkinson,[12] continued these studies, but in addition to measuring the volume of the bile they determined the daily excretion of bile acids as cholates, cholesterol and pigment. Under standard conditions without return of the excreted bile, the output of these various biliary constituents was quite constant. The daily output of bile acids varied from 1.2 to 1.9 Gm., but when all the bile was returned to the duodenum the output was increased to 6.5 to 9.0 Gm. From this, Schmidt and his associates concluded that while there is an active enterohepatic circulation of bile acids, from 10 to 15 per cent is lost on each circuit. This loss is compensated by the bile formed endogenously and from the diet, and the output is more or less constant.

Atropine and acetylbetamethylcholine prevented the increase in volume and cholates that normally followed a mixed meal.

Companion studies in patients with bile fistulas have been reported by Zuckerman, Kogut and Jacobi,[13] who observed that in a patient with

12. Schmidt, C. R.; Beazell, J. M.; Berman, A. L.; Ivy, A. C., and Atkinson, A. J.: Studies on the Secretion of Bile, Am. J. Physiol. **126**: 120-135, 1939.

13. Zuckerman, I. C.; Kogut, B., and Jacobi, M.: Studies in Human Biliary Physiology: I. Fasting Rate and Quantity of Bile Secretion, Am. J. Digest. Dis. **6**: 183-185, 1939. Jacobi, M.; Zuckerman, I. C., and Kogut, B.: Studies in Human Biliary Physiology: II. The Effect of Food Factors and Orally Administered Bile on the Rate and Quantity of Bile Secretion, ibid. **6**: 270-274, 1939.

an apparently normal liver the hourly rate of flow was fairly regular except for slight diminution during the night. The rate of secretion was not affected by changes in the intake of water. When carbohydrate was fed, there was no increase in the volume of bile. A mixed hospital diet or a diet high in fat produced a moderate increase in the output of bile, but the most marked change followed the use of a diet high in protein. The oral administration of bile produced a further increase in the output of bile that was in most instances independent of the food. When a maximal choleresis had been produced by a high protein diet, bile was less effective in increasing this response.

The insertion of a T tube and drainage of the common bile duct permit the study of human bile. During the past ten years there has been an increasing number of such reports. For the most part these reports have been concerned with the secretion of bile salts by the liver during the first week or two after the insertion of the drainage tube.[14] Greene, Hotz, Carter and Twiss,[15] who have made the most recent study of this problem, point out that there is general agreement that when the patient has had no evidence of hepatic disease or the latter is minimal there is a temporary reduction in the concentration of cholates in the bile followed after two to three days by a progressive return to normal levels. This drop apparently is due to the individual or combined effects of a variety

14. (*a*) Greene, C. H.; Walters, W., and Frederickson, C. H.: The Composition of the Bile Following the Relief of Biliary Obstruction, J. Clin. Investigation **9**: 295-310, 1930. (*b*) Walters, W.; Greene, C. H., and Frederickson, C. H.: The Composition of the Bile Following the Relief of Biliary Obstruction: Report of a Series of Illustrative Cases, Ann. Surg. **91**: 686-693, 1930. (*c*) Sterner, R. F.; Bartle, H. J., and Lyon, B. B. V.: Chologogue Effect of Intravenous Injection of Sodium Dehydrocholate, Am. J. M. Sc. **182**: 822-839, 1931. (*d*) Ravdin, I. S.; Johnston, C. G.; Riegel, C., and Wright, S. L.: A Study of Human Liver Bile After Release of Common Duct Obstruction, J. Clin. Investigation **12**:659-672, 1933. (*e*) Breusch, F., and Johnston, C. G.: Zum Verschwinden und Wiedererscheinen der Gallensäuren in der Galle bei vorübergehendem Choledochusverschluss, Klin. Wchnschr. **13**:1856-1857, 1934. (*f*) Kohlstaedt, K. G., and Helmer, O. M.: The Effect of Oral Administration of Bile Salts on Composition of Human Fistula Bile, Am. J. Digest. Dis. & Nutrition **4**:306-312, 1937. (*g*) Doubilet, H.: Hepatic Excretion in Man of the Various Bile Acids Following Their Oral Administration, Proc. Soc. Exper. Biol. & Med. **36**:50-52, 1937. (*h*) Gray, H. K.; Butsch, W. L., and McGowan, J. M.: Effect of Biliary Operations on the Liver: Their Relation to the Concentration of Bile Acids in the Bile, Arch. Surg. **37**:609-618 (Oct.) 1938. (*i*) Gray, H. K.; McGowan, J. M.; Nettrour, W. S., and Bollman, J. L.: Hepatic Damage in Biliary Disease: Its Relation to the Concentration of Bile Acids in the Bile, ibid. **37**:790-799 (Nov.) 1938.

15. Greene, C. H.; Hotz, R.; Carter, R. F., and Twiss, J. R.: The Post-Operative Concentration of Bile Salts in Human Bile, Am. J. Surg., 1940, to be published.

of different factors. The anesthetic agent and the duration of anesthesia, the local as well as the constitutional effects of the operative trauma, the degree of preoperative biliary obstructive and hydrohepatosis and the like factors must all be taken into consideration in interpreting results.

After the initial drop the concentration of cholates in the bile returns toward the normal. The rapidity of this return and the maximal concentration attained during the period of observation are in general inversely proportional to the degree of hepatic damage. The hepatic damage may be evidenced by structural changes as cirrhosis, but Greene, Hotz, Carter and Twiss point out that functional insufficiency may be present without gross pathologic changes. They present evidence that such factors as systemic infection, fever, cholangitis, depletion of bile salts from prolonged drainage or an inadequate supply of carbohydrate will reduce the concentration of cholates in the bile, presumably as a result of functional disturbance. They confirm the report of Greene, Walters and Fredrickson [14a] that the continued failure of the liver to secrete bile acids is evidence of severe functional disturbance and so may be of serious prognostic import.

These studies of the postoperative changes in the concentration of bile salt in the bile are important, for they indicate the multiplicity of factors which affect the functional activity of the liver. The multiplicity of these factors, however, greatly increase the difficulty of determining the ones responsible for the changes in any individual case.

Bile acids, whether administered by mouth or intravenously, are rapidly and quantitatively excreted in the bile. This was suggested by the early studies of Stadelmann,[1] Kühne,[16] and Huppert.[17] Greene and Snell [18] studied the process in more detail and emphasized the rapidity with which intravenously injected bile acids disappeared from the blood stream. The time required for their removal varied with the dose, but even with maximal doses the greater part of the injected bile acids were removed from the blood within thirty minutes. Excretion in the bile likewise was rapid but showed a definite delay, for the peak of the excretion did not come until after the blood had returned to normal. This problem has been studied further by Snell, Greene and

16. Kühne, W.: Beiträge zur Lehre vom Icterus, Virchows Arch. f. path. Anat. **14**:310-356, 1858.

17. Huppert, H.: Ueber das Schicksal der Gallensäuren im Icterus, Arch. d. Heilk. **5**:236-256, 1864.

18. Greene, C. H., and Snell, A. M.: Studies in the Metabolism of the Bile: II. The Sequence of Changes in the Blood and Bile Following the Intravenous Injection of Bile or Its Constituents, J. Biol. Chem. **78**:691-713, 1928.

Rowntree,[19] Bollman and Mann,[20] Chabrol, Cottet and Sallet,[21] and Lichtman,[22] with similar results. More recently it has been reinvestigated by Josephson, Jungner and Rydin,[23] who studied the fate of injected sodium cholate. They used the method of Josephson and Jungner,[24] which permitted determination of both free cholic acid and conjugated bile acid. They found, in confirmation of the earlier studies, that intravenously injected sodium cholate usually was removed from the blood stream in about thirty minutes. The bile acids were less rapidly excreted in the bile, but, interestingly enough, during the first half hour after the injection they were excreted preponderately as free cholic acid, while thereafter a rapidly increasing proportion were conjugated before excretion.

Jungner, Rydin and Josephson,[25] continued this study in experimental jaundice in animals. They found, as Snell, Greene and Rowntree,[19] Bollman and Mann [20] and others did, that the concentration of bile acids in the blood was increased after ligation of the common bile duct. They confirmed the report of Snell, Greene and Rowntree that injected cholates were removed from the blood stream less rapidly than normally. This delay in excretion, however, was much more marked in cases of toxic hepatitis produced by administration of phosphorus or carbon tetrachloride. Their experiments were extended to patients, and Josephson and Larsson [26] found that sodium cholate injected intravenously in man rapidly disappears from the blood and is rapidly and quantitatively excreted by the liver into the bile.

The intravenous injection of a solution of sodium cholate produced a greater rise in the cholic acid content of the blood in patients with

19. Snell, A. M.; Greene, C. H., and Rowntree, L. G.: Diseases of the Liver: Further Studies in Experimental Obstructive Jaundice, Arch. Int. Med. **40**:471-487 (Oct.) 1927.

20. Bollman, J. L., and Mann, F. C.: The Influence of the Liver in the Formation and Destruction of Bile Salts, Am. J. Physiol. **116**:214-224, 1936.

21. Chabrol, E.; Cottet, J., and Sallet, J.: Recherches comparatives sur le pouvoir de concentration du foie et du rein vis-à-vis de l'acide cholalique, Compt. rend. Soc. de biol. **122**:184-186, 1936.

22. Lichtman, S.: The Blood Clearance and Renal Excretion of Bile Acids Following the Intravenous Injection of Cholic and Desoxycholic Acids, Am. J. Physiol. **117**:665-671, 1936.

23. Josephson, B.; Jungner, G., and Rydin, A.: Elimination of Cholic Acids: I. In Healthy Animals, Acta med. Scandinav. **97**:237-253, 1938.

24. Josephson, B., and Jungner, G.: A Comparison of Some Methods for the Determination of Bile Acids in Bile and the Proportion Between the Different Acids, Biochem. J. **30**:1953-1959, 1936.

25. Jungner, G.; Rydin, A., and Josephson, B.: Elimination of Cholic Acids: II. In Experimental Jaundice, Acta med. Scandinav. **97**:254-264, 1938.

26. Josephson, B., and Larsson, H.: Elimination of Cholic Acids: III. In Man, Acta med. Scandinav. **99**:140-146, 1939.

jaundice than in normal persons (Josephson [27]). Patients with obstructive jaundice showed a moderately rapid fall in the cholic acid content of the blood, and the initial level usually was regained at the end of the hour. In patients with acute hepatitis the fall of the blood levels was greatly delayed, and these levels were still elevated at the end of an hour. The tables show considerable overlapping between the different groups, but Josephson recommends the test as valuable in arriving at a differential diagnosis between these two kinds of jaundice.

The study of the effect of bile salts and of various therapeutic agents on the volume and composition of the bile was extended by Schmidt, Beazell, Atkinson and Ivy.[28] The various types of response obtained make it desirable for the physician as well as the physiologist to distinguish between three related effects on the liver and biliary tract:

Cholagogues stimulate the evacuation of the gallbladder and increase the flow of bile into the intestine but do not increase the rate of secretion by the liver.

Hydrocholeretics increase the volume of the bile but do not stimulate the secretion of biliary constituents.

Choleretics produce an increased flow of bile and an increased elimination of biliary constituents.

Schmidt, Beazell, Atkinson and Ivy [28] studied the effect of a number of drugs on the secretion of bile. Mild mercurous chloride has long had a reputation based on its reputed clinical effectiveness in cases of "biliousness" or of "torpid liver." This has not been confirmed by previous experimental work. In the present study, this drug in doses of 100 mg. had no effect on either the volume or the constituents of the bile. Ammonium chloride, urea, calcium gluconate, mucin, chondroitin and sulfanilamide were tested and all found to be without significant effect on the secretion of bile. The authors found, as have other investigators, that sulfanilamide was eliminated in the bile in concentrations that have been reported to be bacteriostatic.

Acetylsalicylic acid increased the volume of the bile by approximately 59 per cent but reduced the excretion of cholates slightly.

Oxidized unconjugated bile acid derivatives, such as the proprietary preparations decholin and ketochol, acted as hydrocholeretics, for they more than doubled the volume of the bile but reduced the excretion of cholates by approximately a third.

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27. Josephson, B.: Elimination of Cholic Acids: IV. In Patients with Liver Disease, J. Clin. Investigation **18**:343-350, 1939.

28. Schmidt, C. R.; Beazell, J. M.; Atkinson, A. J., and Ivy, A. C.: The Effect of Therapeutic Agents on the Volume and the Constituents of Bile, Am. J. Digest. Dis. **5**:613-617, 1938.

Conjugated ketocholanic acids (such as are contained in the proprietary preparation dechacid) had a moderate choleretic action, for the volume of the bile was increased. The excretion of cholates was not changed, but because of the excretion of the administered ketocholanic acids the total bile acid output was increased. These results indicate a specific action of conjugated bile acids which is not shown by the unconjugated preparation, but the authors did not explain the reason for this difference in the two preparations.

Normally occurring conjugated cholic acids (such as are contained in the proprietary preparation bilron) and dog bile were the most satisfactory choleretics, for they produced both an increased flow of bile and an increased excretion of bile salts. In the latter case, it must be remembered that the increase was due to elimination of administered cholates and not to increased synthesis of bile acids.

Effect of Certain Drugs on the Secretion and the Constituents of Bile

	Percental Change Over Control Period			
	Volume	Cholates	Pigment	Cholesterol
Bilron*	+74	+126	+89	+110
Dechacid*	+50	+4	−17	+50
Ketocholt	+144	−28	+35	+80
Decholint	+125	−36	−17	−45
Acetylsalicylic acid	+59	−4	+7	+83
Sulfanilamide	+4	−5	+8	−10
Mild mercurous chloride U. S. P.	0	+8	+16	−83
Linseed oil U. S. P.	+16	+10	+27	+37

* Conjugated bile acids of ox bile.
† Oxidized unconjugated bile acids.

Doubilet [29] also reported a study of the hepatic excretion in dogs following oral administration of various bile acids. When cholic acid was administered, there was a marked increase in the excretion of cholic acid and some increase in that of desoxycholic acid. The administration of desoxycholate increased the excretion of that salt but depressed the excretion of cholate. Doubilet measured the efficiency of the liver by the maximum excretion of bile acids in the smallest volume of bile. When this index was used, the order of decreasing efficiency in the dog was dog bile, ox bile, glycocholic acid, cholic acid, desoxycholic acid and dehydrocholic acid.

Riegel, Ravdin and Prushankin,[30] studied the effect of dehydrocholic acid in 5 dogs and report that in all there was an increase in the volume

29. Doubilet, H.: Hepatic Excretion in the Dog Following Oral Administration of Various Bile Acids, Proc. Soc. Exper. Biol. & Med. **36**:687-690, 1937.

30. Riegel, C.; Ravdin, I. S., and Prushankin, M.: Effect of Sodium Dehydrocholate (Decholin) on Bile Salt, Chloride and Cholesterol of Bile in Dogs, Proc. Soc. Exper. Biol. & Med. **41**:392-395, 1939.

of bile, with 71 per cent as the average. There was little change in the excretion of cholesterol but a slight (20 per cent) increase in the excretion of cholates. The last finding is at variance with the results of Doubilet [29] and of Schmidt and his co-workers.[28] While there was a slight change in the cholates, the more marked increase in the volume of bile still seems to classify the response as hydrocholeretic.

The rational therapeutic use of bile salts depends on an understanding of their functions and activities in the body. These have been discussed in detail in a recent article by Ivy and Berman.[31] These investigators point out that:

1. Bile salts promote the formation of bile. They increase the volume of bile and the output of cholesterol and bile salts but do not affect the excretion of pigment. All, or all but about 10 per cent, of administered natural bile salts are reexcreted in the bile.

2. Bile salts, by keeping fatty acids in solution, may act to prevent precipitation of cholesterol and fatty acids in the gallbladder.

3. Natural bile salts aid in the digestion and absorption of fats.

4. Natural bile salts facilitate the absorption of iron and calcium and are necessary for the absorption of carotene, of cholesterol and of vitamins D, E and K.

5. Bile salts administered orally have a laxative action.

6. Bile salts are said to play a role in detoxifying bacterial toxins in the intestinal tract.

7. Bile salts may affect the storage of glycogen by the liver.

Ivy and Berman [31] discuss the therapeutic use of bile salts under several headings. They point out that in the absence of bile salts in the intestine oral administration of bile salts is indicated to improve digestion and absorption. The profound digestive and nutritional disturbances observable in patients with complete biliary fistulas or with complete biliary obstruction and the symptomatic relief obtained from the administration of bile salts in adequate dosage are evidence for the truth of this recommendation. The importance of giving bile salts as well as vitamin K in the preoperative preparation of jaundiced patients is recognized. The possible harmfulness of the administration of bile salts to a patient with complete biliary obstruction is considered by Ivy and Berman. They point out that clinical experience has demonstrated that oral administration for short periods of time is without evident deleterious effects. They obtained similar results in a few prolonged animal experiments. The earlier studies of Brakefield and

31. Ivy, A. C., and Berman, A. L.: The Rationale of Bile Salt Therapy in Biliary Tract Disease, Minnesota Med. **22**:815-820, 1939.

Schmidt [32] and the more recent ones of Mann and Bollman, showing that in dogs with obstructive jaundice there is rapid excretion of orally administered bile acids in the urine, may explain the apparent absence of toxic effects in such patients.

We wish to emphasize the difference between the administration of bile salts in adequate dosage in the presence of a demonstrated deficiency of bile in the intestine and the widespread popular use of bile-containing pills for the relief of "biliousness" or a "sluggish liver." Too often the condition which the patients seek to correct is one of constipation, and the therapeutic benefit experienced is due to the presence in the preparation of active cathartics, such as aloin, phenolphthalein and the like, and not to the minute amounts of bile salts which are included.

In disease of the biliary tract without acute hepatitis, bile salts are administered to flush the biliary passages with a copious flow of bile of low viscosity. This use of bile salts is rational so far as the bile ducts are concerned, for, as Ivy and Berman indicate, a brisk flow of bile through the hepatic ducts would tend to prevent ascent of infection. We agree as to the value of the administration of bile salts as a postoperative measure in cases in which T tube drainage of an infected common bile duct has been instituted. Because of the hydrocholeretic effect of bile salts, it is possible that the derivatives of oxidized bile acids, such as ketochol and decholin, are preferable to the natural bile acids in this condition. Flushing of the ducts is less certain in the patient who has not been operated on, for theoretically a hypertonic sphincter of Oddi might prevent a free flow of bile. However, Ivy and Goldman [33] point out that spasm of the sphincter is less readily produced if the liver is secreting freely.

Flushing of the gallbladder is a different problem from flushing of the bile ducts, and Ivy and Berman point out that the extent to which the administration of bile will change the chemical constitution of bile in the gallbladder and flush out the gallbladder is uncertain. It also must be remembered that in cases of either acute or chronic cholecystitis in which the gallbladder does not fill, a copious flow of bile could accomplish only a flushing of the bile ducts.

In the presence of disease of the biliary tract and acute hepatitis the use of bile salts has been implied to be of benefit by a number of clinical observers. Ivy and Berman insist that until more unequivocal observations become available they doubt the wisdom of bile salt therapy in

32. Brakefield, J. L., and Schmidt, C. L. A.: Studies on the Synthesis and Elimination of Certain Bile Components in Obstructive Jaundice, J. Biol. Chem. **67**:523, 1926.

33. Ivy, A. C., and Goldman, L.: Physiology of the Biliary Tract, J. A. M. A. **113**:2413-2417 (Dec. 30) 1939.

such conditions except for the purpose of improving intestinal absorption. The previously reported studies have shown that the presence of cholangitis reduces or abolishes the choleretic effect of bile salt preparations and that injected bile salts are not removed from the blood stream at the normal rate. We have been informed of a case of possible acute yellow atrophy following the intravenous administration of a preparation of oxidized bile salts. Under these conditions we wish to second this plea for caution in the therapeutic use of bile salts except when it can be shown that there are specific scientific indications for such use.

LEPTOSPIROSIS ICTEROHAEMORRHAGICA

Leptospirosis icterohaemorrhagica (Weil's disease, spirochetal jaundice) is an infection not of the liver alone but of all the organs of the body. Jaundice may be present, but it occurs in not more than 60 or 65 per cent of the serologically or bacteriologically proved cases.[34] Warrant for the consideration of this systemic infection in a review of the literature on diseases of the liver and biliary tract is derived partly from the traditional association of icterus with Weil's disease, which is reflected in the deceptive but much used synonym "spirochetal jaundice," and partly from the need for considering Weil's disease in the differential diagnosis of hepatitis.

The first adequate description of the clinical syndrome was formulated by Adolph Weil,[35] soon followed by Fiedler.[36] This was some three decades before the discovery of the causative agent, Leptospira icterohaemorrhagiae, by Inada and others [37] in Japan and by Uhlenhuth and Fromme [38] in Germany. During the war of 1914-1918, knowledge of the infection grew by rapid stages out of a wide experience with the disease in soldiers. The extended reports in German [38] and in French [39]

34. (*a*) Walch-Sorgdrager, B.: Leptospiroses, Bull. Health Organ., League of Nations **8**:143-386, 1939. (*b*) Davidson, L. S. P., and Smith, J.: Weil's Disease in the North-East of Scotland: Account of One Hundred and Four Cases, Brit. M. J. **2**:753-757, 1939.

35. Weil, A.: Ueber eine eigenthümliche, mit Milztumor, Icterus und Nephritis einhergehende, acute Infectionskrankheit, Deutsches Arch. f. klin. Med. **39**:209-232, 1886.

36. Fiedler, A.: Zur Weil'schen Krankheit, Deutsches Arch. f. klin. Med. **42**: 261-294, 1888.

37. Inada, R.; Ido, Y.; Hoki, R.; Kaneko, R., and Ito, H.: Etiology, Mode of Infection and Specific Therapy of Weil's Disease (Spirochaetosis Icterohaemorrhagica), J. Exper. Med. **23**:377-402, 1916.

38. Uhlenhuth, P., and Fromme, W.: Untersuchungen über die Aetiologie, Immunität und spezifische Behandlung der Weilschen Krankheit (Icterus infectiosus), Ztschr. f. Immunitätsforsch. u. exper. Therap. **25**:317-480, 1916.

39. Martin, L., and Pettit, A.: Spirochétose ictérohémorragique, Paris, Masson & Cie, 1919.

which resulted are important source references, which have been supplemented but not supplanted by more recent monographs.[40]

On etiologic and clinical grounds, five general types of human leptospirosis can be differentiated.[34a] The type identified as Weil's disease, caused by invasion of L. icterohaemorrhagiae, is usually characterized by an abrupt onset, with fever, vomiting, great prostration and severe myalgia and, after a few days, by the appearance of jaundice.

Jaundice, hepatomegaly, hemorrhagic manifestations, anemia, leukocytosis, albuminuria and retention of nitrogen are classic findings at the end of the first week. The illness is commonly severe and is often prolonged by a febrile relapse in the third or fourth week. Death terminates about 1 case in 9; hepatic, renal or cardiac damage may be the cause. Without icterus, however, the prognosis is favorable; so that the fatality rate in Weil's disease with jaundice is perhaps 1 in 6.

Weil's disease may follow an atypical course. Meningeal symptoms sometimes predominate. In an instance reported by Murgatroyd,[41] evidence of meningeal involvement developed four months after the beginning of the illness, and leptospiras were recovered from the cerebrospinal fluid and urine twenty-five and thirty-three weeks, respectively, after the onset. Leptospirosis with marked signs of meningeal invasion has only recently been reported in the United States,[42] but the condition should be considered in the differential diagnosis of meningitis in cases in which no organisms can be demonstrated in the cerebrospinal fluid by the usual staining and cultural technics.

A second type of leptospirosis found in Europe and America [43] is due not to L. icterohaemorrhagiae but to Leptospira canicola, the canine species. Leptospirosis of this type is usually anicteric, and meningeal signs may be prominent. The remaining three types of leptospiral infection include the swamp fever of central Europe, the seven day fever of Japan and other infections not found in America.

In the transmission of leptospirosis icterohaemorrhagica the rat is an important agent. Leptospiras pathogenic for guinea pigs are shed in the urine of a variable proportion of these rodents. In one recent

40. Uhlenhuth, P., and Fromme, W., in Kolle, W.; Kraus, R., and Uhlenhuth, P.: Handbuch der pathogenen Mikroorganismen, ed. 3, Jena, Gustav Fischer, 1930, vol. 7, pt. 1, pp. 487-660. Walch-Sorgdrager.[34a]

41. Murgatroyd, F.: (*a*) Chronic Meningitis in Weil's Disease, Brit. M. J. **1**:7-11, 1937; (*b*) Further Note on a Case of Chronic Leptospiral Meningitis, ibid. **1**:445-446, 1939.

42. Haschec, W., and Tobey, F. J.: A Case of Weil's Disease, J. A. M. A. **113**:1319-1321 (Sept. 30) 1939.

43. Meyer, K. F.; Stewart-Anderson, B., and Eddie, B.: Canine Leptospirosis in the United States, J. Am. Vet. M. A. **95**:710-729, 1939.

survey J. Smith [44] found such leptospiras in the kidneys of 27.3 per cent of 117 rats brought to the city hospital laboratory in Aberdeen, Scotland. There was a higher incidence of carriers among the full-grown rats than among the young animals. A positive seroreaction was present in the blood of 87.5 per cent of the rats from whose kidneys virulent leptospiras were isolated, but a positive reaction was also obtained in 24.7 per cent of the animals whose kidneys yielded none. The presence of immune bodies in the blood serum of rats has therefore no direct correlation with the carrier state.

Manual workers in trades which attract rats are particularly exposed to infection.[45]. Fiedler [36] commented on the fact that 9 of the 12 victims observed by him were butchers. Miners in Scotland,[46] sewer workers in London [47] and Glasgow,[48] fish cutters in Aberdeen [46] and cane cutters in Australia [49] suffer from Weil's disease, and a British departmental committee in a report to the Home Secretary in 1936 recommended that Weil's disease be thenceforth scheduled as an industrial infection.[50]

One of the first patients with Weil's disease seen in New York was a sewer worker,[51] and 2 sewer workers in New York in whom the disease was recognized during 1938 and 1939 died of it.[52] Two fish cutters in New York contracted the infection, and compensation was awarded both for a disease arising out of or in the course of employment.[53]

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44. Smith, J.: Leptospiral Infections in Rats: Presence of Specific Leptospiral Immune Bodies in Serum and Their Relationship to Carrier Conditions, J. Hyg. **38**:521-526, 1938.

45. Fairley, N. H.: Leptospirosis in the British Empire, Acta Convent. tertii de trop. atque malar. morbis **1**:387-395, 1938.

46. (*a*) Gulland, G. L., and Buchanan, G.: Spirochaetosis Icterohaemorrhagica in East Lothian, Brit. M. J. **1**:313-314, 1924. (*b*) Buchanan, G.: Spirochaetosis Icterohaemorrhagica, ibid. **2**:990-993, 1924; Spirochaetal Jaundice, Medical Research Council, Special Report Series, no. 113, London, His Majesty's Stationery Office, 1927.

47. Fairley, N. H.: Weil's Disease Among Sewer Workers in London, Brit. M. J. **2**:10-14, 1934.

48. Stuart, R. D.: Weil's Disease in Glasgow Sewer Workers, Brit. M. J. **1**: 324-326, 1939.

49. (*a*) Morrissey, G. C.: The Occurrence of Leptospirosis (Weil's Disease) in Australia, M. J. Australia **2**:496, 1934. (*b*) Drew, J. G.: An Account of Weil's Disease in Queensland, Brit. M. J. **2**:1142-1143, 1934.

50. Home Office, Departmental Committee on Compensation for Industrial Diseases, Third Report to the Right Honourable The Secretary of State for the Home Department, London, His Majesty's Stationery Office, 1936.

51. Cushing, E. H.: Leptospirosis Icterohaemorrhagica, J. A. M. A. **89**:1041-1043 (Sept. 24) 1927.

52. Farrell, E.; Tiffany, E., and Rosenthal, M.: Unpublished data.

53. Farrell, E.: Weil's Disease: Compensable Infection in New York State, New York State J. Med. **39**:1969-1972, 1939.

Apart from occupational associations such as those just cited, Weil's disease has frequently occurred after accidental immersion,[54] though no instances of this sort have been recorded yet in the American scientific literature.

Leptospirosis icterohaemorrhagica is recognized far more often in Europe than in America. In Paris the disease is one *d'observation courante,*[55] and single cases of the classic type now attract too little attention to be reported in detail.[56] In Holland 374 cases were established between 1924 and 1938,[34a] and there have been at least 248 adequately diagnosed cases of Weil's disease in Great Britain since 1922.[34b] In the United States not all the proved cases have been reported, nor have all the reported cases been satisfactorily established by recovery and full identification of the causative organism or by satisfactory demonstration of specific immune properties in the blood serum. Recognition of the disease lags, although the work of Meyer [57] and others must eventually lead to a wider appreciation of the nature of this infection and to some reliable estimation of its extent.

The diagnosis of Weil's disease is a laboratory problem dependent for its solution on the alertness of the clinical staff, measured by the alacrity with which the clinical diagnosis is arrived at, on close ward-laboratory cooperation and on the experience of the bacteriologist in the isolation of the organism. Inoculation of guinea pigs with the blood in the first week or with the urine thereafter is the most valuable single diagnostic procedure, but serologic methods of diagnosis are also employed.

In the serologic diagnosis of Weil's disease some modification of the agglutination-lysis test may be used, but considerable experience is required for its reliable performance and interpretation.[58] The antibody titer may rise rapidly late in the third week of disease and reach a level of 1 : 40,000 or more by the end of the fifth week.[59] This level may be maintained for about three weeks; then it falls during a month or so to a much lower mark, at which it may remain for a number of years.

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54. Schüffner, W.: Recent Work on Leptospirosis, Tr. Roy. Soc. Trop. Med. & Hyg. **28**:7-37, 1934.

55. Troisier, J.; Bariéty, M., and Brouet, G.: Spirochétose ictérohémorragique après morsure de rat: Méningite purulente, Bull. et mém. Soc. méd. d. hôp. de Paris **50**:1451-1458, 1934.

56. Brumpt, E.: Personal communication to the author.

57. Meyer, K. F.; Stewart-Anderson, B., and Eddie, B.: Epidemiology of Leptospirosis, Am. J. Pub. Health **29**:347-353, 1939.

58. Brown, H. C., and Broom, J. C.: Observations on the Agglutination Test for Weil's Disease, Brit. M. J. **1**:1178-1179, 1939.

59. Kisker, A.: Ueber den Verlauf des Agglutinationstiters bei Weilscher Krankheit, Ztschr. f. Immunitätsforsch. u. exper. Therap. **85**:383-391, 1935.

Macroscopic agglutination tests [60] and complement fixation tests [61] have also been introduced. In performing serologic tests in cases in which leptospirosis is suspected, it is well to use both L. icterohaemorrhagiae and L. canicola as antigens. In certain cases testing with various strains of L. icterohaemorrhagiae may be necessary for exact identification of the immune bodies found in the patient's serum. Conservative interpretation of single reports should be a rigid rule.

Important practical points in the diagnosis of leptospirosis by inoculation of animals have recently been stressed by workers, who urge the use of guinea pigs weighing less than 175 Gm.[62] or even nursling animals.[43] The animal first inoculated may show no leptospiras at autopsy, but repeated subinoculations of material from successive animals may finally lead to the isolation of the organism. Cultivation of leptospiras has been successfully carried out on the chorioallantoic membrane of the chick embryo,[63] but mediums such as Noguchi, Schüffner, Fletcher or Korthof have described serve the usual laboratory needs.

In the differential diagnosis of leptospirosis icterohaemorrhagica with jaundice, many other causes of icterus must be considered. Catarrhal jaundice, biliary obstruction, toxic hepatitis or acute yellow atrophy may be suggested in turn by successive stages of a leptospiral infection. Useful data in the early clinical recognition of Weil's disease are a history of occupational or accidental exposure to infection, signs of systemic invasion, fever, early prostration and myalgia, nephritis, anemia, leukocytosis and hemorrhages.

Small epidemics of leptospirosis icterohaemorrhagica may occur in similarly exposed groups with a common occupational background [64] or with a commonly experienced immersion or other water accident.

60. Pot, A. W.: A Macroscopic Agglutination Test in Weil's Disease, Lancet **1**:1290, 1936. Smith, J., and Tulloch, W. J.: A Macroscopic Agglutination Test for Diagnosis of Weil's Disease, ibid. **2**:846-850, 1937. Brown, H. C.: A Rapid Presumptive Serological Test for Weil's Disease, Brit. M. J. **2**:1183, 1939.

61. Pot, A. W., and Dornickx, C. G. J.: The Complement Fixation Test in the Diagnosis of Weil's Disease, J. Path. & Bact. **43**:367-372, 1936. Gaehtgens, W.: Ueber die praktische Bedeutung der serologischen Untersuchung, insbesondere der Komplementbindungsreaktion, für die Diagnose der Weilschen Krankheit, Ztschr. f. Immunitätsforsch. u. exper. Therap. **96**: 287-319, 1939.

62. Syverton, J. T.; Berry, G. P., and Stiles, W. W.: The Diagnosis of Weil's Disease (Infectious Jaundice), J. Clin. Investigation **17**:522, 1938.

63. Morrow, G.; Syverton, J. T.; Stiles, W. W., and Berry, G. P.: The Growth of Leptospira Icterohemorrhagiae on the Chorio-Allantoic Membrane of the Chick Embryo, Science **88**:384-385, 1938.

64. Davidson and Smith.[34b] Gulland and Buchanan.[46a] Buchanan.[46b] Morrissey.[49a] Drew.[49b]

Institutional epidemics of jaundice have been attributed to Weil's disease [65] and indexed as spirochetal jaundice,[66] but the evidence for a viral cause of infective hepatitis (epidemic catarrhal jaundice)[67] is too convincing to be shaken by anything short of the isolation of L. icterohaemorrhagiae directly from patients or the demonstration of specific antibodies in changing titer in the blood serum of a significant proportion of those affected. Careful studies in the past [68] have failed to demonstrate an etiologic relationship between L. icterohaemorrhagiae and epidemic infectious jaundice. Harmless leptospiras of typical form occur in nature, so the finding of leptospiras of unidentified species in local collections of water during the course of an outbreak of jaundice [69] cannot be regarded as significant.

The genesis of icterus in leptospirosis icterohaemorrhagica is obscure. Kaneko once concluded that the jaundice resulted from intra-acinous biliary obstruction without actual blockage of the bile channels, but he has modified this opinion,[70] following the work of Oka,[71] who decided that cellular dissociation resulted in dilatation and rupture of the bile capillaries, with escape of bile into the general circulation. In Oka's human cases the blood serum gave a direct van den Bergh reaction. In cases of the infection in guinea pigs the reaction is apparently indirect,[72] and the jaundice is attributed to extensive destruction of blood with retention of bilirubin resulting from functional impairment of the liver due to edema of the organ.

Weil's disease and yellow fever are both characterized by hepatitis, but yellow fever causes specific histologic changes in the liver which can be differentiated from those found in leptospirosis icterohaemor-

65. Slesinger, H. A., and Zeligman, I.: Acute Infectious Duodenitis (Infectious Jaundice): Report of Seventy-Six Cases, J. Pediat. **14**:213-219, 1939.

66. Quarterly Cumulative Index Medicus **25**:724, 1939.

67. Findlay, G. M.; MacCallum, F. O., and Murgatroyd, F.: Observations Bearing on the Aetiology of Infective Hepatitis (So-Called Epidemic Catarrhal Jaundice), Tr. Roy. Soc. Trop. Med. & Hyg. **32**:575-586, 1939.

68. Wadsworth, A.; Langworthy, H. V.; Stewart, F. C., and Moore, A.: Infectious Jaundice Occurring in New York State, J. A. M. A. **78**:1120-1121 (April 15) 1922. Langworthy, V., and Moore, A. C.: A Study of Leptospira Icterohaemorrhagiae, J. Infect. Dis. **41**:70-91, 1927.

69. Willett, J. C.; Sigoloff, E., and Pfau, C. L.: An Institutional Outbreak of Epidemic Jaundice, J. A. M. A. **106**:1644-1646 (May 9) 1936.

70. Kaneko, R.: Ueber den Ikterus bei Spirochaetosis ikterohaemorrhagica Inada (Weil'sche Krankheit), Schweiz. med. Wchnschr. **65**:531-532, 1935.

71. Oka, T.: Ueber den Ikterus bei Spirochaetosis icterohaemorrhagica Inada (Weilsche Krankheit), Klin. Wchnschr. **14**:785-786, 1935.

72. Busch, H.: Ueber die Ursache des Ikterus bei der experimentellen Weilschen Krankheit, Beitr. z. path. Anat. u. z. allg. Path. **96**:233-247, 1936.

rhagica.[73] In yellow fever the liver shows hyaline areas of Councilman necrosis, extensive fatty degeneration and cellular dissociation of such an extreme degree that all lobular structure is lost. Councilman necrosis, is never seen in Weil's disease nor is there as much fatty infiltration or such extensive separation of the liver cells.[74] The anatomic differentiation of yellow fever and Weil's disease is particularly important in those parts of the world where the diseases coexist and where through a viscerotome service [75] search is continually being made for silent foci of yellow fever.

The early administration of 30 to 60 cc. of immune serum with an antileptospiral titer of 1:20,000 or more [76] is of prime importance in the treatment of Weil's disease. No commercial antiserum is generally available in the United States but in Europe such serums are widely used.

Prophylactic immunization against Weil's disease has been tried on a large scale in Japan, with apparently favorable results, but vaccination of human subjects in Scotland with 1 to 2 cc. of killed culture caused only small amounts of lytic antibody to appear in the blood stream.[77]

VITAMIN K AND BLOOD COAGULATION

The earlier literature dealing with the relationship between prothrombin deficiency and the bleeding tendency of jaundiced patients and the importance of vitamin K in correcting this disturbance was reported in the review for 1938.[78] Since then, the literature dealing with various phases of this problem has increased voluminously. It has been summarized in detail by Quick [79] and so need not be reviewed

73. Snijders, E. P.: Zur pathologischen Anatomie der Leber bei Gelbfieber und Weilscher Krankheit, in Arbeiten über Tropenkrankheiten und deren Grenzgebiete (Bernard Nocht's Festschrift), Hamburg, Friederichsen, 1937, p. 539.

74. Bablet, J.: Sur le diagnostic différentiel entre la spirochétose ictéro-hémorragique et la fièvre jaune par l'examen histologique du foie, Bull. Office internat. d'hyg. pub. **28**:2346-2353, 1936.

75. Rickard, E. R.: The Organization of the Viscerotome Service of the Brazilian Cooperative Yellow Fever Service, Am. J. Trop. Med. **17**:163-190, 1937.

76. Zimmermann, E., and Arjona, E.: Serologischer Titer und Heilwert der Seren gegen Weilsche Krankheit, Ztschr. f. Immunitätsforsch. u. exper. Therap. **84**:111-117, 1935.

77. Smith, J.: Vaccination of Guinea Pigs and Human Beings Against Leptospiral Infections, J. Hyg. **37**:261-270, 1937.

78. Greene, C. H., and Hotz, R.: Liver and Biliary Tract: A Review for 1938, Arch. Int. Med. **63**:778-808 (April) 1939.

79. Quick, A. J.: A Classification of Hemorrhagic Diseases Due to Defects in the Coagulation Mechanism of the Blood, Based on Recently Published Studies, Am. J. M. Sc. **199**:118-132, 1940.

further at this time. The most important development during the year has been the isolation of vitamin K in crystalline form, the determination of its chemical structure and its chemical synthesis. This goal was reached practically simultaneously by several different groups of investigators,[80] and accounts of this dramatic race have been reported by Fieser [81] and by Doisy and his associates.[82]

These studies established that vitamin K, prepared from alfalfa, is 2-methyl-3 phytyl-1,4-naphthoquinone. An extensive study of the activity of related naphthoquinones showed that 2-methyl-1,4-naphthoquinone was the most active of these and was at least as efficient as the naturally occurring vitamin K. Since it is slightly water soluble, it can be given intravenously. When given by mouth, it may be absorbed more readily than the natural vitamin K. The clinical uses of 2-methyl-1,4-naphthoquinone in the treatment of prothrombin deficiency have been reported by a series of investigators.[83] Doses of from 0.6 to 10 mg. daily have sufficed to control the hemorrhagic phenomenon and restore the blood prothrombin to normal. No toxic effects have been reported and while further study is required, the introduction of the use of this compound into clinical practice apparently represents a real therapeutic triumph.

DIET IN RELATION TO HEPATIC INJURY

The current widespread use of carbohydrate diets in the treatment of jaundice and hepatic disease is based on two scientific premises:

1. The intermediary metabolism and oxidation of carbohydrate make less demands on the liver than the oxidation of either protein or

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80. Binkley, S. B.; Cheney, L. C.; Holcomb, W. F.; McKee, R. W.; Thayer, S. A.; MacCorquodale, D. W., and Doisy, E. A.: The Constitution and Synthesis of Vitamin K_1, J. Am. Chem. Soc. **61**:2558-2559, 1939. Fieser, L. F.; Campbell, W. B.; Fry, E. M., and Gates, M. D.: Synthetic Approach to Vitamin K_1, ibid. **61**:2559, 1939. Almquist, H. J., and Klose, A. A.: Synthetic and Natural Anti-Hemorrhagic Compounds, ibid. **61**:2557-2558, 1939.

81. Fieser, L. F.: The Synthesis of Vitamin K_1, Science **91**:31-36, 1940.

82. Doisy, E. A.; Binkley, S. B.; Thayer, S. A., and McKee, R. W.: Vitamin K, Science **91**:58-62, 1940.

83. Frank, H. A.; Hurwitz, A., and Seligman, A. M.: The Treatment of Hypoprothrombinemia with Synthetic Vitamin K_1, New England J. Med. **221**: 975, 1939. Macfie, J. M.; Bacharach, A. L., and Chance, M. R. A.: Vitamin K Activity of 2-Methyl-1,4-Naphthoquinone and Its Clinical Use in Obstructive Jaundice, Brit. M. J. **2**:1220-1223, 1939. Butt, H. R.; Snell, A. M.; Osterberg, A. E., and Bollman, J. L.: Treatment of Hypoprothrombinemia: Use of Various Synthetic Compounds Exhibiting Antihemorrhagic Activity (Vitamin K_1 Activity), Proc. Staff Meet., Mayo Clin. **15**:69-73, 1940. Rhoads, J. E., and Fliegelman, M. I.: Use of 2-Methyl-1,4-Naphthoquinone (A Synthetic Vitamin K Substitute) in the Treatment of Prothrombin Deficiency, J. A. M. A. **114**:400-401 (Feb. 3) 1940. Sharp, E. A.: Vitamin K Activity of 2-Methyl-1,4-Naphthoquinone, ibid. **114**: 439-440 (Feb. 3) 1940. Broun, G. O., in discussion on Sharp.

fat. The feeding of enough carbohydrate to provide for the caloric requirements of the patient and keep the intermediary metabolism on a carbohydrate basis is therefore one way of putting the liver in a state of physiologic rest.

2. Laboratory animals on diets high in carbohydrate whose livers contain adequate reserves of glycogen are more resistant to the effects of hepatic toxins, such as chloroform.[84]

The older literature was reviewed by Davis and Whipple [85] and need not be considered in detail at the present time.

The experimental study of the effects of diet on the susceptibility of the liver to injury by chloroform has recently been reinvestigated by Goldschmidt, Vars and Ravdin [86] and by Miller and Whipple.[87] Messinger and Hawkins [88] have studied the effect of diet on the susceptibility of the liver to injury by arsphenamine. All are in agreement that fat is injurious, for the susceptibility of the liver to injury increases progressively with an increase in lipids in the liver. Their different experiments were also in agreement in indicating that a diet high in protein markedly reduced the susceptibility of the liver to injury by either chloroform or arsphenamine. Protein depletion by diet or plasmapheresis increased the susceptibility to chloroform as the bodily stores of protein were depleted. Diets high in carbohydrate proved to be beneficial but not quite as effective as those high in protein. Whether the benefit obtained from carbohydrate diets in these experiments was due to a direct effect of the carbohydrate on the liver or to an indirect influence by virtue of an action on protein or to the fact that carbohydrate diets usually reduce the lipid content of the liver is still unsettled.

These experiments are interesting because of the increasing mass of evidence pointing to disturbances in protein metabolism in hepatic

84. Opie, E. L., and Alford, L. B.: The Influence of Diet on Hepatic Necrosis and the Toxicity of Chloroform, J. A. M. A. **62**:895-896 (March 21) 1914; Diet and the Hepatic Lesions of Chloroform, Phosphorus or Alcohol, J. Exper. Med. **21**:1-20, 1915.

85. Davis, N. C., and Whipple, G. H.: The Influence of Fasting and Various Diets on the Liver Injury Effected by Chloroform Anesthesia, Arch. Int. Med. **23**:612-635 (May) 1919.

86. Goldschmidt, S.; Vars, H. M., and Ravdin, I. S.: The Influence of the Foodstuffs upon the Susceptibility of the Liver to Injury by Chloroform and the Probable Mechanism of Their Action, J. Clin. Investigation **18**:277-289, 1939.

87. Miller, L. L., and Whipple, G. H.: Chloroform Liver Injury Increases as Protein Stores Decrease: Studies in Nitrogen Metabolism in These Dogs, Am. J. M. Sc. **199**:204-216, 1940.

88. Messinger, W. J., and Hawkins, W. B.: Arsphenamine Liver Injury Modified by Diet: Protein and Carbohydrate Protective, but Fat Injurious, Am. J. M. Sc. **199**:216-225, 1940.

disease. Changes in the serum protein and hypoproteinemia, apart from prothrombin deficiency, accompany serious diseases of the liver. Such evidence would seem to indicate the desirability of feeding protein-rich diets to patients with hepatic disease.

This evidence, however, should not be accepted without reservations. Hahn, Massen, Nencki and Pavlov [89] and Fischler [90] long ago pointed out the susceptibility of the dog with a damaged liver (Eck fistula) to the feeding of excessive amounts of meat—the so-called "Fleisch intoxication." Mann and Bollman [91] have confirmed these observations. They later found that the feeding of meat extract produced the same effects as meat. It is also noteworthy that Goldschmidt, Vars and Ravdin [86] used casein for their high protein diets. More work designed to compare the effects of meat as contrasted to protein diets is desirable. Until such studies are reported, the clinician wishing to follow the lead of these investigators will increase the protein content of the diet for patients with hepatic disease but will still avoid excessive amounts of protein and choose dairy proteins in preference to meat.

CIRRHOSIS VERSUS FIBROSIS OF THE LIVER

The proper nomenclature of the various types of hepatic diseases is by no means settled, and only too frequently the same term is used to indicate quite different conditions. Gibson and Robertson [92] call attention to the confusion in the use of the term "cirrhosis." They quote numerous authorities and point out that even among pathologists a definition of hepatic cirrhosis acceptable to all is difficult to find. There is general agreement that parenchymal destruction and scarring must be present. There is less agreement on the importance of parenchymal repair. When only parenchymal destruction and scarring are required by the definition of hepatic cirrhosis, it is difficult to exclude numerous conditions not commonly included within this group, for many agents will produce parenchymal destruction and scarring. Gibson and Robertson therefore limit the definition of hepatic cirrhosis to conditions in which there is evidence of parenchymal degeneration and fibrous and nodular parenchymal repair.

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89. Hahn, M.; Massen, V.; Nencki, M., and Pavlov, J.: Die Ecksche Fistel zwischen unterer Hohlvene und Pfortader, Arch. f. exper. Path. u. Pharmakol. **32**:161, 1893.

90. Fischler, F.: Physiologie und Pathologie der Leber nach ihrem heutigen Stande, ed. 2, Berlin, Julius Springer, 1925.

91. Bollman, J. L., and Mann, F. C.: The Physiology of the Impaired Liver, Ergebn. d. Physiol. **38**:445-492, 1936.

92. Gibson, W. R., and Robertson, H. E.: So-Called Biliary Cirrhosis, Arch. Path. **28**:37-48 (July) 1939.

Using this criterion of cirrhosis, they studied a series of cases of so-called biliary cirrhosis following obstructive jaundice. Both their review of the literature and their study of cases indicated that in cases of this type there are parenchymal degenerative changes of various sorts, an increase in the portal connective tissue, an apparent increase in the interlobular ducts, bile thrombi and collections of cells, such as polymorphonuclear leukocytes, in the portal connective tissue. Emphasis is placed on bile stasis, fibrosis of some degree and parenchymal degeneration. The outstanding feature is the parenchymal degeneration. Gibson and Robertson also point out that the results of parenchymal degeneration frequently dominate the clinical picture, so that the prognosis should be guarded unless the biliary obstruction can be relieved and hepatic recovery permitted. They therefore insist that this condition would be more suitably described as *hepatic atrophy*. This would place the emphasis on the parenchymal degeneration associated with biliary obstruction and jaundice.

Gibson and Robertson further report that in not quite 10 per cent of their cases of biliary obstruction true hepatic cirrhosis was present. These cases were characterized by a history of intermittent or fluctuating jaundice. It seems possible, therefore, that in these cases intermittent episodes of obstruction with associated parenchymal destruction alternating with periods of relief from jaundice and consequent opportunity for parenchymal repair may have led to the production of true *hepatic cirrhosis from biliary obstruction.*

It was therefore suggested by Gibson and Roberston that the term "biliary cirrhosis" be dropped. Cases in which hepatic parenchymal damage without signs of regeneration follows obstruction of the bile ducts should be classified as instances of *hepatic atrophy*. Cases of the infrequent combination of biliary obstruction, obstructive jaundice and true hepatic cirrhosis should be classified as *cirrhosis from biliary obstruction*.

The same difficulties of nomenclature arise in connection with the changes in the liver produced by chronic passive congestion, the so-called cardiac cirrhosis. This problem has been reported in detail by Boland and Willius [93] and by Katzin, Waller and Blumgart.[94]

They agree that the most frequent pathologic picture seen in the liver as a result of prolonged or repeated episodes of congestive heart failure is degeneration of the central portion of the lobules with or with-

93. Boland, E. W., and Willius, F. A.: Changes in the Liver Produced by Chronic Passive Congestion, with Special Reference to the Problem of Cardiac Cirrhosis, Arch. Int. Med. **62**:723-739 (Nov.) 1938.

94. Katzin, H. M.; Waller, J. V., and Blumgart, H. L.: "Cardiac Cirrhosis" of the Liver: A Clinical and Pathologic Study, Arch. Int. Med. **64**:457-470 (Sept.) 1939.

out condensation of the reticulum. It is generally assumed that central lobular atrophy results from chronic passive congestion of gradual onset and that necrosis develops when cardiac failure occurs more abruptly or is of greater severity. Boland and Willius [93] found that they could not predict from the clinical history and physical findings whether the liver would show atrophy or necrosis. The possibility of an additional toxic factor in their cases could not be excluded.

In the more severe cases, especially those with a history of multiple episodes of heart failure, there was considerable evidence of condensation and thickening of reticulum, especially in the areas of degeneration. This thickening of the reticulum on occasion went on to true fibrosis. Both authors insist that condensation of reticulum does not warrant the use of the term "cardiac cirrhosis" but accept it as signifying morphologic increase in connective tissue in the liver consequent to congestive failure but point out that clinical cardiac cirrhosis signifies the extreme fibrosis which results from chronic passive congestion and causes evidences of portal obstruction.

If the definition of cirrhosis propounded by Gibson and Robertson, i. e., hepatic degeneration, fibrosis and parenchymal regeneration, be accepted, and we believe it should be, then these cases of Boland and Willius and of Katzin, Waller and Blumgart should be referred to as examples of cardiac fibrosis of the liver and not of cardiac cirrhosis.

Boland and Willius also include in their report a few cases in which in addition to the degenerative changes of chronic passive congestion and fibrous tissue proliferation there were areas of adenomatous regeneration of the few hepatic cells remaining in the collapsed lobules.

There was a history of multiple episodes of cardiac failure, and Boland and Willius suggest that during the intervals of partial cardiac recovery there was fibrosis of the areas of complete lobular destruction while the partially destroyed lobules underwent regenerative changes. These few cases apparently represent cases of true cirrhosis, but even in them the possibility of contributing toxins could not be excluded. Cardiac cirrhosis in the strictest sense must be accepted as a possible clinical and pathologic entity, but these studies emphasize its rarity.

GENERAL TEXTBOOKS

Attention is invited to two monographs recently published which deal with diseases of the gallbladder and biliary tract (Carter, Greene and Twiss [95]; Walters and Snell [96]). Each is primarily a report of the

95. Carter, R. F.; Greene, C. H., and Twiss, J. R.: Diagnosis and Management of Diseases of the Biliary Tract, Philadelphia, Lea & Febiger, 1939.

96. Walters, W., and Snell, A. M.: Disease of the Gallbladder and Bile Ducts, Philadelphia, W. B. Saunders Company, 1940.

experience of its writers. Each presents a statistical study of an extensive surgical experience.

The most noteworthy feature of the two textbooks, however, is the difference in the point of view. The volume of Walters and Snell follows the traditional form and stresses the anatomic and pathologic changes in the gallbladder and biliary tract. Cholecystitis and gallstones are accepted as unfortunate but real conditions. The treatment is surgical, and the operation is reported as curative.

The volume of Carter, Greene and Twiss departs from the traditional in that the point of view is primarily physiologic, and the emphasis is on function rather than on form. They agree that gallstones and a functionless, infected, fibrotic gallbladder represent pathologic entities which necessitate surgical methods of treatment but emphasize that such conditions in many cases apparently arise as the result of a preceding functional disturbance. If the physician can recognize and by appropriate medical therapy correct this functional disturbance, the development of the surgical lesion may be prevented. Furthermore, surgical operation does not always correct the functional disturbance, and the patient requires careful postoperative as well as preoperative medical management. The textbook therefore stresses the selection of diet and the details of medical management. The diagnostic value of duodenal drainage likewise is stressed.

These differences in point of view are determined by the interests of the authors and the different types of clinical material seen by each group. Primarily, the differences are matters of organization and method of presentation. The careful reader will find that in the majority of instances the question of the choice of medical or of surgical methods of treatment and the methods of treatment considered appropriate are the same.

News and Comment

Second Graduate Course in Internal Medicine, Vanderbilt University Medical School.—This course consists of supervised work with patients in the medical outpatient service, including the related specialties; experience in the diagnostic laboratories; assigned reading, seminars and conferences, including pathologic and radiologic conferences and autopsy study, and directed study and seminars in the preclinical sciences, particularly physiology and biochemistry. Special investigation of a particular problem in one of the divisions of internal medicine as the basis of a thesis will be required. The course extends over a period of one year and is open to physicians who have completed an internship, have had an additional year's experience as assistant resident in medicine or its equivalent and are acceptable to the school. The second course begins July 1, 1940. The tuition fee is $300.

Applications for admission and fellowships will be received by the Director of Postgraduate Instruction, Vanderbilt University Medical School, until April 15, 1940.

Three fellowships are available for this course. These fellowships, which provide tuition, board and lodging, are open to those who meet the requirements mentioned and will be awarded on the basis of training and recommendations.

American Heart Association.—The sixteenth scientific sessions of the American Heart Association, Inc., will be held at the Roosevelt Hotel, New York, June 7 and 8. On the first day there will be a program on the heart, and on the second day the program of the Section for the Study of the Peripheral Circulation will be presented.

American Public Health Association.—The sixty-ninth annual meeting of the American Public Health Association will be held in Detroit, October 8 to 11. The Book-Cadillac Hotel will be the headquarters. Dr. Reginald M. Atwater, 50 West Fiftieth Street, New York, is executive secretary.

The Michigan Public Health Association, the American School Health Association, the International Society of Medical Health Officers, the Association of Women in Public Health and a number of other allied and related organizations will meet in conjunction with the association.

The Michigan Committee on Arrangements is headed by Mr. Abner Larned, of Detroit. Dr. Henry F. Vaughan, health commissioner of Detroit, is executive secretary of the committee.

American Association for the Advancement of Oral Diagnosis.—The annual meeting of the American Association for the Advancement of Oral Diagnosis will be held on Oct. 17 and 18, 1940, at the building of the New York Academy of Medicine, 2 East One Hundred and Third Street, New York.

Further information and membership blanks may be procured from Dr. H. Justin Ross, executive office, 515 Madison Avenue, New York.

Industrial Health.—The twenty-fifth annual meeting of the American Association of Industrial Physicians and Surgeons, together with the first annual meeting of the American Industrial Hygiene Association, will be held at Hotel Pennsylvania, New York, June 4 to 7, 1940. Technical and scientific exhibits will be a feature of the convention. The dinner on Thursday evening, June 6, will be the occasion of the presentation of the William S. Knudsen award for the year of 1939-1940.

Book Reviews

Fisiopatologia dello scompenso cronico di circolo. By D. Cesa-Bianchi and M. Calabresi. Pp. 187. Rome: Luigi Pozzi, 1936.

This work digests thoroughly the majority of the recent European and American articles on the pathogenesis of cardiac and circulatory decompensation. The results of studies carried out in the authors' clinic are presented in essence, but no quantitative data are offered. Most of their work has been concerned with the biochemical features of circulatory failure. Much significance is attached by them to the defects of lactic acid metabolism, the oxygen debt and the increased basal metabolic rate of decompensated patients. The authors revel in the paradoxes which are apparent on comparing the theories and facts relating to decompensation. They argue that the majority of the data are complementary, not contradictory. They think that decompensation of the circulation occurs when the cardiac output is inadequate for the tissue needs. The decreased blood supply causes capillary stasis, tissue hypoxia and the formation of acid metabolites. Concurrently with the diminution in output, there must be a damming back of that blood which would normally be ejected. This causes retrograde stasis and venous hypertension and further insults the tissues injured by the hypoxia. This synthesis, then, is a fusion of the theories of forward and backward failure.

Notable omissions from lengthy consideration are the theories of dyspnea that Peabudy, Harrison and others have advanced.

Although the paper was prepared for a clinical congress, the clinical implications of the data are meagerly presented, and no therapeutic deductions are made.

Diseases of the Skin. By Richard L. Sutton and Richard L. Sutton Jr. Tenth edition. Price, $15.00. Pp. 1549, with 1452 illustrations and 21 color plates. St. Louis: The C. V. Mosby Company, 1939.

In this tenth edition the authors have attempted, very successfully, to correlate descriptions and concepts of disorders of the skin with general medicine and biology —to answer the question "What is going on?" rather than to content themselves with classification. This approach has necessitated radical rearrangement and the inclusion of much material not to be found in the ninth edition. Also added are ten color plates and a large number of new illustrations. The bibliography is extensive and includes many additional comments intended primarily for the special student. The book should serve as a valuable work of reference for the internist.

A Textbook of Medicine. By American Authors. Edited by Russell L. Cecil. Fourth edition. Price, $9. Pp. 1,614, with 42 illustrations. Philadelphia: W. B. Saunders Company, 1937.

Cecil's "Textbook of Medicine" has established itself so solidly that the periodic appearance of new editions is taken as a matter of course. In this fourth edition the general scheme and format are preserved, and, as far as the reviewer can see, the various articles have been brought well up to date. The book is to be recommended especially as a miniature system of medicine, most of the articles being written by recognized authorities; but the large number of contributors makes one feel the lack of a uniform point of view. For purposes of general reference there is no better book.

Results Followed Up for Twenty Years After Grafting of the Thyroid in Cases of Myxedematous Creatinism. By Serge Voronoff. Translated by Theodore C. Merrill. Bulletin 492, Société de pathologie comparative, Paris, October 1937.

Case reports are presented of 3 myxedematous cretins each of whom received a thyroid transplant either from his mother or from an ape. The submitted photographs, the data on physical and mental growth and the basal metabolism indicate that the transplanted glands truly "took." The author believes that, aside from the usual precautions taken with glandular transplants, the grafting of the gland to its usual site is important.

Clinical Allergy. By Louis Tuft, M.D. Price, $8. Pp. 711, with 82 illustrations. Philadelphia: W. B. Saunders Company, 1937.

As a number of excellent texts on allergy have appeared in the past few years, one wonders on seeing still another whether it has any novel features. The reviewer is very favorably impressed with Tuft's compact treatise, which is well written and seems to cover the subject in a thorough and yet not extreme manner. Of particular value to the reader and the student are the various excellent illustrations, the summary of much material in tabular form and the charts and diagrams, such as those of the distributions of various pollens.